Ketosis in Domestic Animals

Clinical and experimental observations

By Jesse Sampson

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Bulletin 524 : University of Illinois

Agricultural Experiment Station

ACKNOWLEDGMENT

IN THE PREPARATION of this bulletin the author is indebted to many colleagues for their interest and assistance. He is indebted to Dean Robert Graham of the College of Veterinary Medicine for his encouragement and support, and to other members of the faculty of the College of Veterinary Medicine for generous aid and suggestions, particularly to those in the Department of Veterinary Physiology and Pharmacology.

Special mention should be made of the help given by the following members of the staff: Dr. C. C. Morrill, who supplied the photographs shown in Figs. 1, 4, 5, and 8 (pages 430, 446, and 460); Dr. R. P. Link, who supplied the data shown in Fig. 3 (page 443) and, with Dr. L. E. Boley, furnished the data on ketosis in the horse, page 462; Dr. L. E. Boley and Dr. Vera M. Hanawalt, who assisted in many ways during the collection of data at the Illinois Agricultural Experiment Station; Dr. J. A. Henderson, who directed attention to several references not readily available and made other suggestions. Helpful criticisms were made by Dr. H. H. Mitchell and Dr. T. S. Hamilton of the Laboratory of Animal Nutrition in the Illinois Agricultural Experiment Station.

Former colleagues at Cornell University — Dr. C. E. Hayden, Dr. M. G. Fincher, Dr. J. A. Dye, and Dr. Peter Olafson — gave valuable criticism. To Dr. H. H. Dukes of the same institution the author is indebted for permission to cite unpublished data obtained in experiments conducted by Dr. Dukes and the author in the Department of Veterinary Physiology at the New York State Veterinary College.

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Urbana, Illinois December, 1947

Publications in the Bulletin series report the results of investigations made or sponsored by the Experiment Station

KETOSIS IN DOMESTIC ANIMALS

By JESSE SAMPSON, Professor of Veterinary Research,
Agricultural Experiment Station[a]

INTRODUCTION

KETOSIS may be defined as an abnormal accumulation of the so-called ketone or acetone bodies in the body. *Ketonemia* and *ketonuria* refer to the presence of excess amounts of ketone bodies in the blood and urine respectively. *Acetonemia* has the same meaning as ketonemia and *acetonuria* is used synonymously with ketonuria. The ketone bodies or ketone substances are organic chemical compounds and include acetone, acetoacetic acid, and betahydroxybutyric acid.[47]

Origin of ketone bodies. The formation of ketone bodies is called *ketogenesis.* A unanimity of opinion seems to prevail as regards the source and origin of the ketone bodies. Specifically, authorities on ketosis generally agree that the primary, if not the only, source of the ketone bodies is the liver; furthermore, that the origin of these substances is mainly fat even tho it has been demonstrated that a small number of amino acids, such as phenylalanine and tyrosine, may be a potential source of these compounds. Betahydroxybutyric acid and acetoacetic acid are believed to be partial oxidation products of butyric acid. Acetone is thought to be a derivative of acetoacetic acid by the loss of carbon dioxide.[47]

"Ketolysis" theory. — There are two divergent viewpoints regarding the metabolic process that gives rise to ketone bodies in the body. Apparently the first view, and until recently the more widely accepted, is the theory of "ketolysis."[117, 10] According to this theory fat catabolism, instead of going to completion to form carbon dioxide and water, stops at the ketone stage whenever there is a deficiency of carbohydrate in the metabolic mixture. An important function of carbohydrate metabolism, adherents of the ketolysis theory claim, is that of continuing the catabolism and utilization of the ketone bodies formed during fat catabolism. The ketolysis theory is illustrated by the oft repeated statements that "Fats burn only in the presence of carbohydrates," or "Fats burn in the flame of carbohydrates."

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[a] Also Professor of Veterinary Physiology and Pharmacology in the College of Veterinary Medicine.

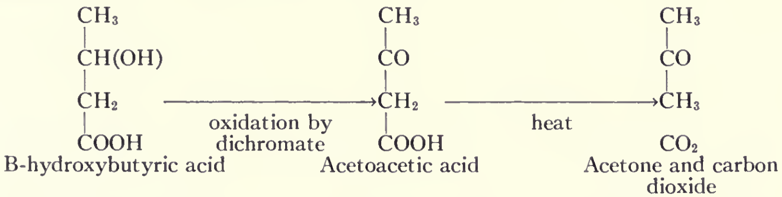
"Antiketogenesis" theory. — The second, and at present the more generally accepted point of view, is the theory of "antiketogenesis."[18, 31] Optimum carbohydrate metabolism, according to this theory, inhibits ketosis not "by increasing the utilization of acetone bodies, but by keeping the production of these bodies down to a minimum (antiketogenesis)."[47] In other words, the first theory maintains that ketosis is inhibited because catabolism (oxidation) of a minimum amount of carbohydrate (glucose) aids catabolism and utilization of fat. The second theory holds that ketosis is inhibited by the simple expedient of increasing carbohydrate catabolism and decreasing fat catabolism. This appears possible only if the liver has a liberal reserve of glycogen.[85, 82] Under certain conditions, discussed under experimental and clinical studies of ketosis in cattle and sheep (pages 422 and 441), the metabolic needs of the body, particularly for carbohydrate, are greatly augmented. During such emergencies the body presumably turns to fat in an effort to compensate for any carbohydrate deficit. As Mirsky[82] puts it, "A diminution in liver glycogen is the essential prerequisite for an increase in fatty acid oxidation, resulting in an accelerated rate of acetone body formation in the liver and a consequent acetonemia."

Chemistry. That the chief source of ketone bodies is fat seems to be well established.[47] It is much less certain, however, just how these substances are produced from fat in the liver. Oxidation of fat *in vivo* apparently begins with hydrolysis of the fat molecule to glycerol and fatty acid. Then further oxidation of these components occurs. Glycerol, which represents about 10 percent of the fat molecule, like glucose, probably gives rise to glycogen in the liver.[47] Biochemists have found great difficulty in following the changes that occur during oxidation of the fatty acid fraction. A theory presented by Knoop in 1904, however, provides a clue to a fundamental reaction which may take place during intermediate fat metabolism. Knoop's theory is that in each step in the breakdown of fatty acids that contain an even number of carbon atoms (those present in natural fats) oxidation occurs at the carbon atom in the Beta-position to the carboxyl group. By this process two carbon atoms are split off in each step until the 4-carbon atom stage is reached. At this stage, acetoacetic acid is one of the products. This acid is then converted to acetic acid, which undergoes further changes to carbon dioxide and water.

A more recent explanation of fatty acid oxidation is known as "beta oxidation-condensation" theory[59] of MacKay and coworkers.

This theory maintains that all fatty acid chains are oxidized at each alternate carbon atom, the molecule splitting at each keto group to form molecules of acetic acid except where a 3-carbon chain remains. Such a chain forms proprionic acid, which can be changed to glucose. Two molecules of acetic acid condense to form acetoacetic acid. For further information on oxidation of fat and the formation of ketone bodies, see discussion by Best and Taylor (1945).[7]

In vitro, oxidation of betahydroxybutyric acid gives rise to acetoacetic acid, and the spontaneous decomposition of acetoacetic acid produces acetone and carbon dioxide. These reactions form the basis of the Van Slyke quantitative method of analysis for ketone bodies in blood and urine. These reactions are shown in the following diagrams from Peters and Van Slyke (1932).[93]



Analysis is first made for preformed acetone and acetoacetic acid. A determination is then made for betahydroxybutyric acid. An alternate procedure is a single determination in which heat and oxidation of betahydroxybutyric acid by the dichromate are allowed to act simultaneously, the result representing the sum of all three ketone substances contained in the aliquot. In other words, by this technic the total amount of ketone bodies is obtained by one distillation. The technic for determining total ketone bodies is a popular procedure because it is time saving. (The Barnes and Wick[4] and the Weichselbaum and Somogyi[141] technics are accurate procedures for the determination of very small amounts of ketone bodies.) A common practice is to express the results obtained by the analysis for either betahydroxybutyric acid or total ketone bodies, as acetone.[93]

Physiologic and pathologic actions. Acetoacetic acid and betahydroxybutyric acid behave like other acids in their effect on the acid-base balance of the body; i.e., they tend to deplete the alkali or base reserves and cause acidosis. In fact, the production of these acids in diabetes mellitus of man may be so great as to lead to severe acidosis (dangerous lowering of the alkali reserve) and coma[94] (see discussions on ketosis of the cow, ewe, and sow, pages 427, 442, 456).

Besides its acidic properties, acetoacetic acid is a toxic substance.[7] Betahydroxybutyric acid, however, is relatively nontoxic. Acetone, on

the other hand, is definitely poisonous to the body. According to Sollmann,[129] acetone given hypodermically to guinea pigs is more toxic than methyl alcohol. Sollmann also states that inhalation of acetone causes dyspnea, a progressive fall in body temperature, respiration, and heart rate in proportion to the concentration of acetone inspired. If guinea pigs inhale vapor containing 1 percent acetone for 48 hours, or 5 percent for 5 to 8 hours, the spleen, lungs, and kidneys become congested. At autopsy, pulmonary edema also is observed.

Altho the ketone bodies are produced by the liver, this organ is apparently not capable of using them. Certain other tissues, particularly muscle, have the ability to utilize these substances.[47] (Shaw and coworkers[122] have shown that B-hydroxybutyric acid is apparently one source of energy for the active mammary gland in the cow.) If the ketone bodies are produced in excess, the body tries to get rid of the surplus by way of excretion thru the kidneys and the lungs. Betahydroxybutyric acid and acetoacetic acid are neutralized and eliminated in the urine largely in the form of sodium, potassium, and ammonium salts. This accounts for the decrease in alkali reserve which is often associated with ketosis. Acetone is eliminated mainly in the urine but also to some extent in the expired air.[94]

It is therefore evident that when the processes of utilization and elimination do not keep pace with the rate at which the ketone bodies are produced, ketosis develops.[59] The danger associated with ketosis is a very real one. According to Sollmann,[129] "It may be so severe that animals die of coma before the fat depots are depleted. The coma is due partly to acidosis, partly to the special toxicity of acetoacetic acid, which causes air hunger or depression of the respiratory center."

I. KETOSIS IN RUMINANTS

Cattle, sheep, and goats are susceptible to ketosis. The economic importance and world-wide distribution of clinical ketosis in the bovine and ovine species is now universally recognized, but much less is known about the importance and incidence of ketosis in the caprine species (see page 455). Apparently nothing at all is known concerning the susceptibility of such ruminants as the camel or members of the deer family to ketosis. It will be no surprise, however, if future studies reveal that some of these ruminants are susceptible to both experimental and spontaneous ketosis, particularly under circumstances comparable to those which characterize the condition in cows and ewes.

The reasons for this belief will be evident when the etiology of ketosis in cattle and sheep is considered.

The ensuing discussion of ketosis of ruminants, especially of cattle and sheep, probably explains why Groenewald, Graf, Bekker, Malan, and Clark,[45] in reporting results of a comprehensive investigation of clinical and experimental pregnancy disease of ewes, concur with the view expressed by Sampson, Gonzaga, and Hayden[110] that ketosis in these species has fundamental similarities, even tho spontaneous ketosis is observed most often in late pregnancy in ewes in contrast to early lactation in cows. McIntosh,[78] in discussing ketosis or acetonemia of cows, also refers to these similarities and states that "In sheep there is a striking counterpart of this disease which is referred to as a Pregnancy Disease."

KETOSIS (ACETONEMIA) IN CATTLE

Acetonemia Is an Old Disease

According to Udall,[137] the nervous form of the disease now known as ketosis or acetonemia of cows was probably recognized as early as 1849 by Landel, who described it under the name of "mania puerperalis." Fleming's[37] classic textbook, *Veterinary Obstetrics,* refers to the reports of Storrar, Harms, Rolls, Robellet, Gunther, and Landel on mania puerperalis of cows. Mr. Robellet's account appeared first in *Recueil de Méd. Vétérinaire* and was later translated and incorporated in a report published by Rolls[103] in *The Veterinary Journal.* Since the nervous form of acetonemia of cows has been mistaken for rabies even in recent times, the report by Robellet is of unusual interest. Furthermore, Robellet employed chloral hydrate therapy, a practice which some veterinarians still follow in treating acetonemia.[116, 98] Robellet described his case as follows:

An affection in a cow, simulating Rabies, cured by chloral. On the 28th of June, 1874, at eleven o'clock p.m., M. Dubost, of Chassaguy, came to ask me to go as soon as possible to attend one of his cows, which was very ill. This cow had calved on the 24th of the same month; parturition had taken place normally, and nothing had been noticed afterwards to indicate either suffering or disease. On the morning of the day I was called, she refused to eat at pasture; the attendant noticed that she left the other animals, and constantly licked her fore legs. In the cowshed she would take no food, and licked herself until about eight o'clock p.m. She then appeared restless, and bit all the things surrounding her. On my arrival, the owner showed me a medium-sized cow, four years old. I approached her cautiously, and found that she really bit her manger, her rack, and food, which she allowed to fall again on the litter without masticating it;

she also seized her breast and fore legs, but without breaking the skin. I tried to ascertain the state of the pulse, and did so without difficulty, the cow apparently not noticing me; the artery was full, pulsations sixty per minute; the eyes, unnaturally open, were red, fixed, haggard, and the pupils dilated; the buccal mucous membrane was slightly inflamed, a frothy saliva surrounding the borders of the lips; respiration was not troubled, the respiratory movements being regular and about twenty per minute. At times the cow stretched out her fore parts, bellowed, pawed the ground with her fore feet, and seemed to defy an invisible enemy. Taking advantage of her placing herself in one of these attitudes, I held a prong-handle to her; she seized it frantically and bit it, shaking her head violently.

These symptoms caused me to suspect Rabies. This, in fact, was the diagnosis I gave, and I asked the owner if a mad dog had not been seen in the neighborhood. His distinct denial, and the assurance with which he declared his cow had not been bitten, slightly embarrassed me. Nevertheless, I doubled the chain she was fixed by, separated her from the others, and then thought of treatment. I had read, some days before, the researches of M. M. Horand and Peuch on chloral; I remembered M. Peuch's experiments with it in Canine Rabies; and notwithstanding his failures, relying on the well-known efficacy of this drug against any form of nervous excitement, I administered an ounce and a half (50 grammes) in two drenches of tea. I gave them myself, one a quarter of an hour after the other, taking care to administer them gently, in order that the liquid might go directly into the abomasum, and the effect be prompt. Several minutes after the administration of the second drench, the cow, which had continued showing the same symptoms, hung her head, and without staggering, fell like an inert mass on the ground, then rose at once of her own accord. Ten minutes after, the same occurrence took place; the cow again fell suddenly, but she at once jumped up again. The animal remained in the same excited condition. I left her about two o'clock a.m. The next day, at ten o'clock a.m., I returned, but what was my astonishment to find that all the alarming symptoms of the night before had disappeared; the cow was lying on her near side, and was peacefully ruminating. On my entry she rose and began to eat her litter; there was no fever; the expression of the eye was mild, and apart from slight weakness and prostration, the cow might have been considered cured. The owner told me that half-an-hour after my departure she appeared to suffer less, and not so frequently; then having fallen a third time, she became drowsy, and remained lying about three hours, after which she rose apparently well.

This observation is interesting in several ways: first, what disease had I to deal with? Rabies alone presents the symptoms described above. The cow, however, recovered, and this diagnosis must therefore be false. Was this nervous excitement dependent on epileptic vertigo, or simply nervous lactation? We doubt it. Can we ascribe it to acute Enteritis, or to any poisoning, or to both these? No. There was neither Tympanitis, Diarrhoea, nor Colic. One fact is certain, that it was a disease greatly resembling Rabies, yet not really it. . . . This observation also shows the efficacy of chloral. The dose of an ounce and a half was not sufficient to produce sleep; but the prostration of strength and the drowsiness were

favorable to recovery. My father, veterinary surgeon at Briguais, now an old practitioner, tells me that during his long experience he has only met with two cases of this singular affectation; the subjects were also cows newly calved; both recovered, but more slowly, doubtless owing to his not having at his disposal so powerful an anaesthetic as chloral.

Rolls, commenting that he recalls no similar case reported in English veterinary publications, gives the following account of his experience with the disease which Fleming called mania puerperalis:

In the evening of January 12th, 1874, I was sent for in great haste to visit a cow at W——— B———. On my arrival, I elicited the following details from the cowman. The animal was five years old, had calved about a fortnight before, during the night, and had eaten her "cleansing." She had gone on favourably until the last day or two, when, as she seemed rather poorly, he had given her a "red drench," which had not, however, purged her. She had also recently been turned out into a fresh piece of grass, while it was covered with white frost. *Her calf had been removed the night before.*

Sym

According to Rolls, the cow showed the following symptoms:

Very wild excited expression; eyes staring; ears warm; pulse full, rather strong and quick; jaws continually moving, as if in the act of biting; frothing at the mouth; the under part of the tongue purple and livid-looking. The movement of the jaws cannot be stopped by attempting to hold them together. When left quietly to herself, she continually gnaws her fore legs, without, however, making a wound; when interrupted, she will gnaw the manger, the woodwork of the place, or anything presented to her. Thus, if hay was offered her she would seize it, masticate it with the continuous and violent movement of the jaws, and swallow it. When offered to her, she also swallowed some sloppy bran-mash and chilled water. Although she has eaten nothing the greater part of the day, she looks full; and there is the peculiar sour smell often met with in cows suffering from gastric derangement, but specially when it occurs shortly after parturition. The bowels are in fair condition.

The impression left on my mind at this period was that the cow was suffering from gastric derangement, and that the nervous phenomena depended on, and originated in, that disorder. Treatment: — Venesection from the subcutaneous abdominal vein, to the extent of a gallon. Administer extract belladonna ʒ ij., to be repeated if necessary, ol. lini, Oj. About three hours after my departure the convulsive movements ceased, and the animal seemed much better. 14th. — Cow much better; no convulsive movements, but there is still an excited expression about her. Gave a dose of ext. belladonna. 15th, etc. — Cow goes on favourably, feeds and ruminates, but copious purgation has commenced; this continuing for two days, I thought it advisable to check it, and for that purpose gave tinct. opii. *cum* pulv. gentian rad. in rice gruel. This speedily had the desired effect, and after two or three days the animal was turned out to grass.

March 9th, 1875. I was stopped on my morning round to see the same cow. The cowman reports: she calved a fortnight since, has not eaten her "cleansing," as she was closely watched. Yesterday her calf was taken

from her and this morning she was found suffering from a similar attack; the jaws moving in the same way, and gnawing her fore legs, but not so violently. He had bled her from the jugular vein, and before he left home she seemed easier. On my arrival I found the cow looking very wild and excited; pupils of eyes normal; ears warm; pulse eighty per minute, full and strong; frothy about the mouth; under part of the tongue livid; grinding her teeth occasionally; the fore legs were wet and covered with saliva from her gnawing them — this she has now ceased. The bowels were in normal condition. Gave her an opiate I happened to have with me; ordered bran-mashes to keep her bowels regular. The cow was no further trouble, and was turned out to grass on the 11th inst.

In some remarks pertinent to his own observations as well as to those reported by Robellet, Rolls says:

The two preceding cases will, I think, be at once admitted to be identical in their nature. In my patient's first attack, gastro-intestinal derangement was no doubt present for some few days before the nervous affection appeared. That such was the case is shown by the symptoms, sour smell, slight tympany, the excessive purgation on the third day, which was totally out of proportion to the amount of aperient medicine given, also the cowman's statement that she had not seemed very well for a day or two. On the second occasion, not the slightest gastro-intestinal derangement could be detected, and the transition from health to disease appears to have been sudden.

In M. Robellet's case, no symptoms of derangement of the digestive organs were noticed, and in his speculative queries as to the true nature of this affection, he appends to that special question a strong negative. We may, therefore, I think, conclude that the view I first took of the affection being connected with derangement of the digestive apparatus is erroneous, and that its true nature consists in extreme nervous excitement caused by the removal of the calf. The breeder informs me that she showed no symptoms of any disease, nor any special excitement, after her previous calvings, and was sold by him, with calf at foot, to present owner early in 1873.

Fleming's[37] comments on these cases are enlightening. Referring to the cause of the disease, he states:

Rolls thought that in the case he describes, depriving the animal of its
Cause calf was the cause of the attack; Harms ascribes the symptoms to chills, which cause brain congestion; while Storrar looks upon the malady as epileptic, dyspeptic, and uterine. The animal affected has calved some few days previously — say from four to fourteen, or even more days; she has been heartily eating her food; giving milk . . . [rich in cream]; and the usual uterine lochial discharge has been suppressed. Or the case might be thus stated: An excessive drain upon the system by the mammary glands, causing, perhaps the suppression of the uterine cleansing, with the peculiar smell about the animal, and more marked in her milk, which is referred to by Mr. Rolls, followed by a more or less severely developed attack of indigestion. These causes act upon the nervous centres, so as to produce the extraordinary excitement which has been described. The dyspeptic signs are the more prominently shown — such as a desire to eat any thing un-

clean in preference to good food, or coarse straw in preference to roots or hay. The bowels become torpid, and the supply of milk nearly ceases.

We can scarcely bring ourselves to believe that this condition is due to psychial influences, and are rather inclined to attribute it to cerebral irritation from some physical cause — either indigestion, constipation, or deranged circulation in the brain, and connected with the parturient state.

In regard to treatment, Fleming offers this advice:

If indigestion or constipation are present, purgatives should be administered, with stimulant or tonic medicines, according to the indications. When there is much fury or excitement, narcotics in large doses may be given — the best, perhaps, being chloral hydrate. Great attention must be paid to the diet. Günther abstracted blood in large quantity, and gave extract of stramonium. He, also, on the supposition that the brain was congested, applied strong stimulants to the back of the head and to the spine.

Under the subject "Depraved Appetite," Law[65] presumably discusses ketosis when he refers to "digestive disorder" as a contributing cause, altho he seems to imply that traumatic pericarditis may be a more serious sequel of pica than is the presence of ketone bodies in blood and urine. Among the other causes of pica or depraved appetite, Law mentions heredity, soil, and hence crop deficiencies, heavy demands on cows for secretion of milk and reproduction, and permanent stabling of cows during winter and spring months. For opinions of others as to the cause or causes of the disease now specifically referred to as either acetonemia or ketosis of cows, see etiology, page 417.

Economic Importance

Accurate appraisal of the economic loss caused by ketosis of cows is difficult because the disease is not associated with high mortality as is true of clinical ketosis of ewes. Observations reported from widely separated areas, however, suggest that clinical ketosis is responsible for a heavy loss to the dairy industry, especially in lower milk production. It is also of considerable importance to the beef-cattle industry as it occurs frequently in the heavier-milking cows of the beef breeds.[58] Severely affected cows, if not given prompt and specific treatment, may die, or if they eventually recover, are often unprofitable producers and have a low market value if sold for slaughter. Sjollema and Van Der Zande,[128] in describing symptoms and calling attention to the economic importance of acetonemia of cows in Holland, state:

Other symptoms are a small and capricious appetite, an impression of seeking some particular substance, pica, dry faeces, forced and deep breathing, irregular rumination, and a decreased milk yield. The animals lose much weight, become thin and listless, and the gait is often more or less paretic. . . . In exceptional cases, if diarrhoea appears, the disturbance may cause death.

In America, Truax[136] of Iowa has said:

Acetonemia of dairy cows, though comparatively rare, is a doubly serious condition. Constitutional damage to affected cows is grave and sometimes fatal while milk yields from herds wherein this queer disease exists are, more often than not, unfit for use. Because of these factors, owners of such cattle become greatly discouraged, often to a point approaching complete disgust.

Truax described ketosis in a herd of 18 head of dairy cattle, 12 of which were mature cows. Three of the 12 cows were affected with ketosis but manifested "no unusual symptoms other than the characteristic odor of acetone in the milk and breath. However, the owner emphasized that, at the onset, they had suffered a bad loss in weight. In his own words, 'they had all gone to pieces.' "

Magill,[72] of South Carolina, writing on field observations of bovine acetonemia said:

I feel that not very many of these cases will die even though no treatment is given. However, they do not milk more than one-half to three-fourths of their normal flow and many will continue to yield the repellent acetone odor in the milk for a long time, rendering it unfit for table use.

Fincher,[35] reporting on acetonemia as he has observed it in the dairy herds in the state of New York, said:

This disturbance of metabolism is thought by some to be unimportant because relatively few cattle die from uncomplicated acetonemia. The owners of good dairy herds soon learn to appreciate the importance of this disease when one takes the trouble to diagnose it regularly and accurately. Our clients recall cases which showed symptoms of acetonemia and finally died under treatment that we applied before acetonemia was recognized. . . . The loss in production of milk because of acetonemia is not to be ignored. Cows with acetonemia have to be discarded because of emaciation and low milk production, and in many of these instances an early diagnosis and the use of a specific treatment for acetonemia would have kept the cow in production.

Duncan, Huffman, and Tobin,[29] in reporting on ketosis of cows in the state of Michigan state: "Since this disease became recognized, its economic importance from the standpoint of loss in flesh, milk production, and production of off-flavored milk has become more apparent." According to Knodt, Shaw, and White[61] of Connecticut, "The problem of ketosis is becoming of as great concern to dairymen as it has been to professional workers. . . . " And in the opinion of Forbes,[38] "The economic features of the problem stem from the facts that in dairy cows the milk production and the general condition of the animal are severely affected, while in the pregnant ewe death is likely to occur or the young, when born, are unthrifty."

Incidence

From what has been said concerning the economic importance of acetonemia to the dairy industry, it seems evident that ketosis of cows occurs wherever dairying is practiced. There is also other evidence of its wide distribution. Hayes,[49] who was among the first to describe acetonemia in America, reported it from Texas; while Alston,[2] about the same time, reported it from Mississippi. In his first report on acetonemia, Alston named the disease "palsy after calving." Ketosis or acetonemia of cows has been reported at various times in recent years from many other states. Among these, not in chronological order, have been reports from Alabama, Louisiana, Tennessee, Oklahoma, Georgia, Florida, Kentucky, Indiana, Ohio, Kansas, Idaho, Missouri, Pennsylvania, New Jersey, Massachusetts, Wisconsin, Minnesota, Nebraska, and California. Presumably clinical ketosis or acetonemia of cows occurs more frequently in the dairy herds of the South[90] and East than elsewhere; yet Sampson and Boley[107] have reported that acetonemia is not uncommon in the dairy herds of Illinois, a state located in the corn belt of the United States.

As mentioned earlier, Sjollema and Van Der Zande[128] reported acetonemia in the dairy herds of Holland, and Hupka[56] stated that acetonemia undoubtedly was a common disease of dairy cattle in Germany. It has also been reported from such other countries as Denmark,[137] Norway,[13] Sweden,[137] England,[137] and Canada.[78] Messervy,[79] of the Royal Veterinary College of London, has made the significant statement that "Though acetonemia has been known to exist in [the Island of] Jersey for over 40 years it was described as dyspepsia."

Progress in Study of Etiology

Ketonemia and hypoglycemia. Practically all investigators who have studied spontaneous, or clinical, ketosis of cows and ewes have concluded that ketonemia and hypoglycemia are the most constant changes found in the blood of affected animals. In severe ketosis of cows (acetonemia) and of ewes (pregnancy disease) hypoglycemia is usually pronounced. Ordinarily, therefore, an inverse relationship exists between the levels of total ketone bodies and sugar of the blood in ketosis of ruminants.[113, 45, 102]

Quantitative data on ketone bodies in blood and urine of cows affected with clinical ketosis were, so far as the author is aware, first published by Sjollema and Van Der Zande[128] in Holland, and by Sampson and Errington,[109] and Sampson, Gonzaga, and Hayden[110] in

America. The data of Sampson and coworkers were obtained by chemical analysis of the blood of a Jersey heifer which, so far as could be determined, was affected with uncomplicated acetonemia. The heifer showed symptoms commonly associated with the so-called "digestive" type of acetonemia: lack of appetite, sharp reduction of milk flow, rapid loss of body weight, listlessness, and elimination of dry, hard, mucus-covered feces. Normal parturition had occurred several weeks before symptoms became noticeable. A concentration of 64 milligrams of total ketone bodies for each 100 cubic milliliters of blood was found before treatment was given.

Altho in the majority of cases of acetonemia of cows the level of total ketone bodies of the blood is less than 64 milligrams for each 100 cubic milliliters, values greater than this are not uncommon, as shown in Table 1. Such values are in sharp contrast to those found for normal bovine blood, which ordinarily contains less than 5 milligrams

TABLE 1. — TOTAL KETONE BODIES AND SUGAR IN BLOOD OF HEALTHY COWS AND COWS AFFECTED WITH KETOSIS (ACETONEMIA)
(Ketone bodies expressed as acetone[a])

Healthy cows			Cows affected with ketosis		
Cow	Ketone bodies	Sugar	Cow	Ketone bodies	Sugar
	mg/100 ml	mg/100 ml		mg/100 ml	mg/100 ml
10	7.07	40.68	1	176.10	No detn.
435	.74	53.11	2	70.93	36.16
556	.62	50.85	3	21.95	42.94
689	2.23	55.37	4	22.06	44.07
691	.99	54.24	5	56.79	36.16
725	2.11	40.68	6	45.01	18.08
438	2.98	36.16	7	32.12	42.94
540	0	59.89	8	27.90	36.16
721	.99	42.94	9	49.35	31.64
Average	2.21	48.21	Average	55.80	28.51

[a] Van Slyke's method[93] was employed for all determinations of ketone bodies given in this and other tables reporting Illinois data.

percent and a maximum of approximately 6 to 7 milligrams percent[20, 110, 12, 29, 62, 108] (see also Table 1). In this connection, contrary to the opinions expressed by Eden and Green,[32] and Duncan *et al.*,[29] Sampson and Hayden[113] believe that cows affected with even mild ketonemia, i.e., when the content of total ketone bodies of the blood may be only 10 milligrams percent, usually manifest one or more symptoms observed in typical acetonemia, such as capricious appetite, reduced milk yield, and excessive loss of body weight.

If it is accepted that ketonemia and hypoglycemia are the primary changes in the blood of cows affected with spontaneous ketosis, the

question arises as to their significance. Some believe that ketonemia is of minor importance and that the symptoms can be attributed largely to low blood sugar. For example, Hupka[56] states that the syndrome of acetonemia of cows seems to be due to hypoglycemia. That hypoglycemia is the cause of symptoms observed in acetonemia, he says, is supported by the low sugar content of the blood and knowledge of the effects of large doses of insulin in producing intense hypoglycemia in humans and animals. Hupka cites observations of Kruse who found that large doses of insulin given to apparently healthy cows caused such symptoms as depression, reeling, pressing forward, muscle twitching, salivation, licking, and deranged vision. (Pica, or depraved appetite, so often observed in cows affected with ketosis is probably associated with hypoglycemia. Best and Taylor[7] say: "It will be remembered that one of the early symptoms observed in experimental animals and also in human subjects after the administration of insulin is an increase in hunger. In animals an attempt to consume material of little nutritive value which under ordinary conditions they would not attempt to eat is often observed.")

According to Hupka, the belief that acetonemia of cows is primarily a hypoglycemic condition is also supported by the knowledge that symptoms soon disappear after sugar is given. Roepke[102] also is inclined to look upon hypoglycemia as much more significant than ketonemia in acetonemia of cows. He says:

A low blood sugar level is another important finding in the more severe cases. The severity of the clinical symptoms, especially the nervous reactions, muscular incoordination and depression, follow rather closely the degree of hypoglycemia. Nervous reactions and muscular incoördination usually do not appear until blood sugar levels are reduced to about one-half that of normal. Nerve cells use only carbohydrate as a source of energy, and, therefore, suffer quickly when a low blood sugar level develops. The prompt improvement frequently observed after the intravenous administration of dextrose also serves to illustrate the close relationship between hypoglycemia and some of the clinical symptoms. The severity of the clinical symptoms does not parallel closely the blood ketone concentration. Cows with high blood ketone values do not necessarily show muscular incoördination and nervous reactions, unless the blood sugar values are low, as mentioned above.

The importance of low blood sugar could hardly be stated more clearly. Altho the author agrees with Hupka and Roepke that hypoglycemia is highly significant in acetonemia of cows, he is persuaded that ketonemia also is highly significant because clinical ketosis has been observed in cows with blood-sugar values in the normal range[110, 12, 107] (see also Table 1). Furthermore such evidence of re-

covery as normal appetite and milk flow often does not appear until ketonemia is dissipated.[107]

Reference to statements made on page 409 of the pathologic physiology of ketosis furnishes evidence as to the deleterious effects of the ketone bodies. It is well to bear in mind that even tho the ketone substances are looked upon as normal products of fat metabolism, it does not follow that an excess of these compounds, especially acetone and acetoacetic acid, in the blood and tissues can be tolerated with impunity.[129, 19] For example, Mirsky,[82] in discussing the question of toxicity of the ketone bodies in diabetes mellitus of humans says, "For some time minor controversies occurred with reference to the relative importance of the acidosis or the toxic effects of the acetone bodies themselves in the production of the coma. Today the physician is aware that both are important."

Sampson and Hayden[113] have called attention to the fact that ketonemia in severe acetonemia of cows and in pregnancy disease of ewes is often as intense as the ketonemia found in severe diabetes mellitus of man. Limited data show that approximately 50 percent of the total concentration of ketone bodies in spontaneous ketosis of cows and ewes is in the form of preformed acetone and acetoacetic acid.[45, 123] The toxic effects of acetone and acetoacetic acid can be demonstrated by injecting relatively small amounts of these compounds into experimental animals.[105]

The writer disagrees with the opinion frequently expressed that ketonemia occurs in a large number of diseases of animals. So far as he is aware, evidence has not been presented to show that significant ketonemia occurs in steers, bulls, wethers, and rams no matter what the disease with which they are affected. A mild ketonemia apparently may develop in white-snakeroot poisoning.[24]

A significant spontaneous ketosis of the ovine and bovine species in this country is limited almost exclusively to females during pregnancy and lactation (see also pages 431 and 449). This opinion is based on published and unpublished data collected by the writer and his associates since 1930, first at Cornell University and later at the University of Illinois. Hendershot[50] has reported that severe ketosis occurs in cattle of different ages and different sex in certain areas of the Hawaiian Islands when the animals must subsist on forage known as the Kiawe bean.

The brilliant studies of Mann and his associates[73, 74] proved that the liver is the primary source of blood sugar, exclusive of that which enters the blood from the intestine.

Furthermore, as McCleod[77] has indicated, it is not likely that the lactic acid which escapes into the blood during muscular contraction and is later changed to glycogen in the liver, as shown by Cori,[23] is a significant source of sugar except in violent exercise. This apparently leaves but one other important source, the conversion of protein to glucose in the liver. That this process presumably can and probably does occur is evidenced by the refractoriness of mature animals to the development of dangerous hypoglycemia during prolonged fasting.[84, 28] In emergencies, however, such as may exist in late pregnancy and the first few weeks of lactation, when there is an increased demand for energy,[102, 38, 45] the available reserve of sugar stored in the liver as glycogen may be rapidly depleted and, unless a liberal supply of glucose is maintained by the ingestion of large amounts of sugars and starches, a transitory lowering of blood sugar develops. While this is in progress, the liver, as Mirsky[82] points out, presumably turns to fat in an attempt to make up for the carbohydrate deficit, and increased catabolism of fat causes excess production of ketone bodies. This state of affairs, if not arrested by ingestion and absorption of either carbohydrate or a potential carbohydrate former (e.g., protein) continues until more and more energy is derived from tissue protein and less from depot fat. Concurrent with the increase in protein catabolism, there is apparently an increase in available sugar and any lowering of the sugar content of the blood is again restored to normal level.[84] Since protein is more antiketogenic than ketogenic,[77] an increase in protein catabolism might well account for the observed tendency of cows with mild ketosis to recover without treatment.[120] Similarly, the tendency of ewes affected with *mild* pregnancy disease to recover after the lambs are born may possibly be attributed in part to the antiketogenic effect of the breakdown of tissue protein as well as, presumably, to the sudden tho transitory reduction in the demand for energy immediately following parturition.

Is there experimental evidence to support the view that carbohydrate deficiency is the cause of hypoglycemia and ketonemia in ruminants? The answer is that experimental evidence supports this view as regards ewes but only limited experimental data are available to answer the question with respect to cows. From a carefully planned experiment to study the influence of diet on ketonemia in pregnant ewes, Fraser, Godden, Snook, and Thomson[40] draw these conclusions:

> An inverse correlation exists between ketonaemia on the one hand, and body weight and blood sugar on the other. Thus, with a fall in body weight there is observed a corresponding fall in the blood sugar level, while at the same time the ketones in the blood increase. . . . It is evident from these

figures that ketonaemia tends to increase with underfeeding, still more with fasting, and to decrease when food intake is increased.

Reference is again made to the observations of Fraser *et al.* in the discussion on ketosis, or pregnancy disease, of ewes (page 442). Similarly, Groenewald, Graf, Bekker, Malan, and Clark,[45] in a critical study of experimentally induced ketosis or pregnancy disease of ewes, found that intense hypoglycemia and severe ketonemia occurred in ewes that were underfed; whereas in ewes that received an adequate ration, sugar and ketones of the blood remained at normal levels. For further comment on the observations of Groenewald and coworkers, see page 441.

Forbes[38] demonstrated that under certain conditions fasting caused a definite lowering of sugar and a significant rise in ketones of the blood. For the production of experimental ketosis in cows and goats Forbes states that it is necessary that —

> . . . the animals be in good condition and that they be nearing parturition or in early lactation. The first requirement should be met so that the fasting animal may catabolize a sufficient amount of fat that ketone bodies in excess of the amount utilizable will be formed. This is borne out by consideration of the clinical experiences in ketosis and pregnancy disease in which the most severe cases have occurred in the animals that were in better condition at the start of the attack.

Furthermore, according to Forbes, the reason that —

> . . . the dairy cow is more susceptible to ketosis during early lactation than during late pregnancy, when goats and sheep are more susceptible, might be explained by the fact that years of selective breeding have developed an animal that produces several times more milk than she was originally destined to do, and this strain on her system is even greater than that of pregnancy. That this strain is great, and that the cow is not completely adapted to it, is shown by the consistently negative mineral, nitrogen, and energy balances associated with the onset of a heavy lactation. Also, it has been shown that during lactation the blood lipids are significantly higher than during pregnancy in the dairy cow — the values tending to rise quickly parallel to the milk flow and then to drop gradually as the milk flow decreases. This is evidence of the intense fat metabolism associated with a heavy lactation and explains in part why a ketosis can be most readily produced at this time in the dairy cow.

From the clinical standpoint the bulk of available evidence supports the belief that carbohydrate deficiency is the primary cause of hypoglycemia and ketosis in ruminants. Evidence on this point with reference to ewes appears in the discussion of pregnancy disease.

Evidence for and against the carbohydrate or caloric deficit point of view for ketosis of cows is presented here. In support of this conception may be cited the opinions of Forbes,[38] whose observations have

already been referred to, and those of Sampson and Hayden,[112] Henderson,[51] Roepke,[102] Duncan, Huffman, and Tobin,[29] and McIntosh.[78] Sampson and Hayden have stated:

It is highly probable that the essential cause of the severe ketosis associated with acetonemia of milk cows and pregnancy disease of ewes is a disturbance in carbohydrate metabolism, due either to a lack of sufficient carbohydrate or carbohydrate forming material in the ration or to an insufficient supply of available carbohydrate stored in the body [liver].

It is evident, of course, that enough carbohydrate or carbohydrate-forming material may be supplied by the ration and yet carbohydrate deficiency may develop if the demands of the body for glucose are high and the animal stops eating or if for some reason the carbohydrate ingested is not assimilated and made available.

Henderson, in reporting a case of severe ketosis in a high-producing Holstein-Friesian cow, says that apparently she secreted the dry matter represented by approximately 25 pounds of milk daily at the expense of her body tissues.

The fat, protein, and minerals which go to form this quantity of milk might well be sacrificed without great inconvenience, but any considerable negative carbohydrate balance cannot long be tolerated without serious depletion of the [glycogen] reserves [in the liver], and presumably ketosis.

Duncan, Huffman, and Tobin made a detailed study of acetonemia in a purebred herd of dairy cattle in which a large number of the cows in lactation were affected. Duncan *et al.* concluded:

The results would seem to indicate that high-producing cows on ordinary roughage rations may be constantly demanding quickly soluble sugars to satisfy the demand for endogenous carbohydrate metabolism, which cannot be supplied indefinitely thru the catabolism of proteins and fats and diminishing deposits of glycogen, since the hay ordinarily used for stall feeding is usually low in sugar in comparison to pasture plants. This may account for the tendency for ketosis to occur more frequently in cattle during the winter months.

Roepke said:

The more severe cases of acetonemia, which continue for three or four weeks and require a number of intravenous dextrose injections to keep them going along reasonably well, occur usually from 10 days to six weeks after calving. Such cows are usually high-producing cows and the disease occurs at a time when the stimulus for milk production is at its maximum. At this time there is a tendency for a cow to utilize more energy for milk production than can be replenished by the amount of food she is able to consume and digest. High-producing cows during the early lactation period usually draw on their carbohydrate and fat reserves and show a weight loss.

McIntosh has this to say:

When high producing cows commence to secrete large quantities of milk

following parturition, sugar is removed very rapidly from the blood as it traverses the mammary gland. For this reason an increased amount of sugar must be available and be constantly added to the blood. This sugar is obtained in part from the food the animal consumes and from the liver glycogen. If the cow can eat enough sugar-producing food and her liver can maintain the necessary glycogen level to meet with the lactation demand nothing will happen. On the other hand, if the blood sugar level is not maintained energy requirements will have to be provided from some other source and it is then that the oxidation of fat in extraordinary amount commences. The mobilization of these fat substances (ketones) may exceed their removal from the blood and in turn lead to an excessive accumulation of them resulting in ketosis. It is, therefore, believed that the failure of the liver to maintain an adequate level of glycogen is a major factor in the onset of ketosis. This may be the result of an inadequate diet or an error in the formulation of the diet or that the character of the diet is such that it interferes with normal functioning of the liver and may even cause retrogressive changes in it.

The belief that carbohydrate or caloric deficit is the major contributing cause of the development of ketosis of cows has been questioned by Shaw[118] because in one herd of high-producing Holstein cattle, the incidence of ketosis was apparently not reduced by feeding molasses (one or two pints daily in addition to the regular ration for several weeks in late pregnancy) prior to parturition. On the basis of these observations Shaw concluded that "since the liberal feeding of molasses prior to parturition failed to prevent ketosis, a soluble carbohydrate deficiency is not indicated." Shaw recognizes, however, that apparently there is a close relation between the amount of liver glycogen and the development of ketosis in cows because he also says:

It is apparent that the hypoglycemia observed following parturition is closely associated with the initiation of milk secretion and the demands of the mammary gland for blood glucose. Under normal conditions these demands are apparently not excessive. With depleted glycogen reserves, the sudden increase in the utilization of glucose by the gland would be expected to lower the liver glycogen content still further. . . . A sudden increase in the mobilization of glucose undoubtedly takes place with the initiation of milk secretion and probably is a major factor in the development of ketosis. This could account for the development of ketosis if the liver glycogen was low at the time of parturition. Some degree of more or less permanent damage to the liver might account for the failure of many cases to respond readily to glucose therapy. The annual recurrence of severe ketosis in some cows following parturition could also be explained on this basis.

It will be noted that altho Shaw's interpretations are not in accord with the belief that a carbohydrate or caloric deficit is probably the most significant influence, they closely parallel other opinions concerning the relation of liver glycogen to spontaneous ketosis of ruminants.

With reference to the amount of oxidizable carbohydrate available to the fasting ruminant, Ritzman and Benedict[97] made the interesting observation that the sheep, altho carrying a large amount of material in the rumen,

> . . . is similar to other animals in its reaction to fasting, in that its supply of oxidizable carbohydrate (glycogen) is small and a respiratory quotient indicating predominantly fat combustion is reached not far from forty-eight hours after ingestion of food.

Despite the fact that the reserve glycogen stored in the liver is important in maintaining an adequate concentration of glucose in the blood when sugar is not absorbed from the intestine for any considerable length of time, it is well to recognize the transitory nature of this source of sugar. In discussing the significance of hepatic glycogen, Soskin[130] says:

> The liver glycogen thus represents a reserve of carbohydrate upon which the liver may draw quickly while the gluconeogenetic processes are accelerating to an adequate rate. While this reserve is important for temporary emergencies, it is not always sufficiently appreciated that it represents a rather small amount of carbohydrate as compared to the body's daily requirements. If we assume, for example, that a man weighing 70 kgm. with a liver weight of 1800 gm. has an average good glycogen store of about 6 percent, this would mean a total liver glycogen of 108 gm. If gluconeogenesis were to cease, this amount of carbohydrate could supply the requirements of his extra hepatic tissues (roughly ¼ gm. kgm. per hour) for about 6 hours only. The relative importance of the gluconeogenetic processes as compared to the liver glycogen reserve is obvious.

On the basis of the foregoing statement by Soskin that if gluconeogenesis were to come to a standstill, the reserve glycogen stored in the liver of man would supply the extra-hepatic need for sugar for only six hours, it seems equally obvious that the stored glycogen in the liver of either the cow or the ewe is also inadequate to supply the extra-hepatic requirements for sugar for more than a short time. Apparently, as Ritzman and Benedict have shown, decreasing amounts of sugar are absorbed from the intestinal tract of the ruminant (sheep) 48 to 72 hours after the last ingestion of feed (when fed an ordinary ration) and then the animal must depend upon the reserve glycogen in the liver for glucose until the process of gluconeogenesis is sufficiently accelerated to supply the demand.

As to the amount of available glycogen present in the bovine liver, the data of Knodt and Petersen[60] indicate that the dairy cow probably has a low reserve. These investigators analyzed the livers of 20 cows and found the glycogen content ranged from .15 to .38 percent, with an average of only .25 percent. Knodt and Petersen state that these

low values may have been accounted for in part by the effect of fasting "since these cows had probably not been fed for at least 24 hours previous to slaughter." Roderick, Harshfield, and Merchant[101] found that livers of six apparently normal pregnant ewes contained from 3.36 to 4.29 percent glycogen with an average of 3.77 percent. These data are on a fresh basis.

According to Sisson and Grossman,[126] the average weight of the bovine liver is approximately 5 kilograms and that of the ovine liver about 600 grams. Using the average value of .25 percent of Knodt and Petersen for liver glycogen content, a simple calculation reveals that the liver of the cow contains only about 12.5 grams of reserve glycogen. This is probably too low, as Knodt and Petersen have indicated, but even if we use the value for sheep, i.e., 3.77 percent, and the calculation made on the basis of a 5-kilogram liver, less than 200 grams of glycogen would be available for emergency needs. The 600-gram liver of the ewe would contain only 22.6 grams of available glycogen, assuming that the average glycogen content is 3.77 percent.

It seems clear, therefore, that in advanced pregnancy or during heavy lactation, when there is an increasing demand for glucose, the store of reserve glycogen in the liver would soon be depleted if it were not replenished from the glucose entering the blood from the intestinal tract. Even if a maximum storage of liver glycogen, certainly a desirable state, were effected by feeding liberal amounts of concentrated, easily assimilated carbonaceous feeds, such as molasses or corn sugar, with ordinary rations composed of cereal grains and roughage or silage, depletion of reserve liver glycogen would presumably occur *whenever the pregnant or heavily lactating cow or ewe went "off feed" or was fed an inadequate ration, especially a ration low in energy or caloric value.*

A number of investigators who have studied ketosis, or pregnancy disease, of sheep believe that it is often beneficial to supplement the ration fed to ewes during the latter part of gestation with small amounts of molasses or other easily assimilated carbohydrate.[75, 45] Presumably there is just as much justification for feeding several pounds of easily assimilated molasses or corn sugar with the average ration of concentrates and roughage fed to the high-producing dairy cow during the early part of lactation (or even before the onset of lactation, i.e., before parturition) when she is most susceptible to the development of ketosis, as there is to feed concentrated, readily available molasses or sugar to the pregnant ewe. Molasses may be beneficial primarily because of its effect as an appetizer to increase the palatability of the ration. It also has a laxative effect.

The practice of feeding molasses or sugar should not, however, be considered an infallible measure for preventing ketosis in either cows or ewes. This is suggested by the report of Ritzman and Benedict and by the knowledge that only a relatively small reserve of glycogen can be stored in the liver under the most favorable circumstances. Furthermore, Hamilton[46a] has reported that when glucose, to the extent of approximately 20 percent of the energy intake of steers and sheep, is added to the ration, the microorganisms in the rumen apparently ferment this sugar entirely to the exclusion of cellulose, which otherwise would be fermented in comparable amounts.

Other changes in chemical constituents of blood. In severe ketosis of the bovine there is often a lowering of the carbon dioxide combining power or alkali reserve of the blood, but in the majority of cases values are within the normal range.[128, 112, 29, 32] Acidosis is therefore not believed to be an important factor, but the true significance of changes in the acid-base equilibrium of the blood and tissues is still unknown. There is often a marked increase in blood cholesterol,[128] but in uncomplicated ketosis of cows normal values are usually found for calcium, inorganic phosphorus, magnesium, chlorides, and nonprotein nitrogen.[128, 110, 112, 29]

Changes in urine. Sjollema and Van Der Zande[128] reported as much as 10 to 13 grams of total ketone bodies per kilogram of urine in acetonemia in contrast to .1 to .7 gram per kilogram of normal urine of cows. High concentrations of ketone bodies in urine of cows affected with ketosis also have been reported by Sampson and associates, Duncan *et al.*,[29] and others.[38, 123] Sjollema's maximum value of .7 gram is probably too high because the urine of healthy cows rarely contains as much as .3 gram per liter.[112, 61] Urine of cows affected with ketosis is often acid because of the high content of ketone substances. For the same reason, there is usually a great increase in the content of ammonia in the urine of these cows[110] (see page 410). Sjollema and Van Der Zande reported 10 to 20 times more calcium per liter of urine of cows affected with acetonemia than in normal bovine urine.[a] In some cases of ketosis of cows the urine is colorless while in others the normal straw color seems to be intensified.

Changes in milk. That milk produced by cows affected with ketosis may contain an appreciable amount of ketone substances has been observed by both practicing veterinarians and research workers. For example, Sjollema and Van Der Zande[128] reported 3 to 4.5 grams

[a] The author has observed, however, that many cows affected with acetonemia excrete relatively small amounts of calcium in the urine.

of total ketone bodies per kilogram in the milk of some cows affected with acetonemia. In contrast, milk of normal cows contains only traces of ketone bodies.[29, 107, 62]

Total ketone bodies in milk of cows before recovery from acetonemia are shown below (Illinois data, ketone bodies expressed as acetone):

	mg/100 ml		mg/100 ml
Cow 1	31.25	Cow 4	5.46
Cow 2	7.44	Cow 5	8.68
Cow 3	30.38	Cow 6	17.86

No ketone bodies were found after these cows recovered.

Relation of vitamins to ketosis of ruminants. No critical evidence has as yet been presented to indicate the existence of any relationship between vitamins and ketosis of animals. The possibility of vitamin B_1 deficiency in acetonemia of cows has been suggested by Carlström,[16] but it is difficult to explain a deficiency of this vitamin because the concentrates of rations fed to dairy cows are ordinarily well fortified with B_1 and also because the mature ruminant has the ability to synthesize this vitamin in the rumen.[28, 76] Patton[90, 91, 92] believes that acetonemia is a vitamin A deficiency, but this belief is based upon meager and conflicting evidence. For a review of this evidence, the reader is referred to the original articles published by Patton.

Attention is called to the difficulty which may be encountered when an attempt is made to produce experimentally vitamin A deficiency in the dairy cow. For example, Schmidt[115] found that it required approximately 24 months to produce symptoms of vitamin A deficiency in five Jersey cows fed a ration which was extremely deficient in vitamin A or its precursor, carotene. According to Schmidt, night blindness is the first noticeable symptom to develop in the syndrome of vitamin A deficiency, and it seems significant that so far as the author is aware night blindness has never been described as a symptom of uncomplicated acetonemia of cows. (Freer and Hayden[42] mention temporary blindness in one case of acetonemia.) Schmidt also emphasizes swellings, particularly of the front legs, in vitamin A deficiency. This symptom is rarely, if ever, observed in acetonemia of cows. Furthermore, ketosis has occurred in cows that were fed liberal amounts of green alfalfa and clover hay and even in cows with access to green pasture,[107, 12, 123, 98] altho it seems evident that it is less likely to develop during the pasture season than during the months when cows are kept indoors and stall-fed.[29] In this connection the observations reported by Sutton and Soldner[134] on the seasonal con-

centration of vitamin A in the blood of dairy cattle are of interest. These investigators found that vitamin A content of the blood of dairy cows was highest during the months of October to March and lowest during May and June.

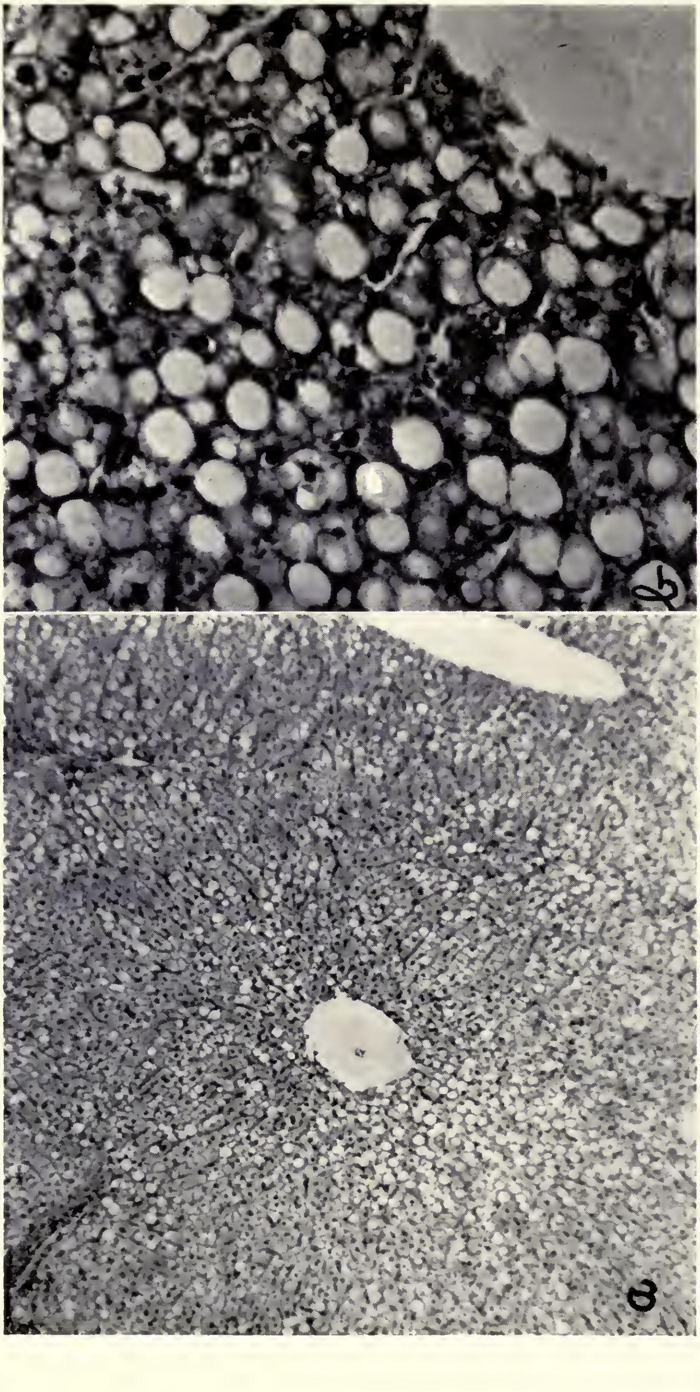
It is now recognized that determinations for vitamin A in blood may not provide sufficient evidence for diagnosing a vitamin A disturbance.[87, 88] Apparently the liver may contain appreciable amounts of vitamin A even tho an animal is in a state bordering on cachexia. Moore, cited by Linton and Brownlee,[67] found that extreme emaciation in rats did not necessarily reduce the vitamin A reserves of the liver; and Linton[67] has shown that livers of hens and geese which had been starved to death contained large reserves of vitamin A in spite of the rigors of starvation. Further comment on vitamin A and ketosis is given on pages 436, 437, 453.

Endocrine organs and ketosis of animals.[a] With the possible exception of the dog, evidence so far accumulated does not indicate that natural, or spontaneous, ketosis of animals is associated with a specific dysfunction of any endocrine organ. Diabetes mellitus has been reported occasionally in dogs, but we are aware of only one report of spontaneous diabetes occurring in ruminants, one in swine, and none in other species of domestic animals. The sole case of diabetes in ruminants was described by Sjollema and Van Der Zande[128] in a cow. Spontaneous, or natural, ketosis has been studied in the cow, ewe, goat, and sow, and in none of these has it been shown that a lack of insulin and impairment of the animal's ability to utilize carbohydrate were involved.

A possible relationship has been suggested between dysfunction of the pituitary gland and ketosis of cows,[36] but more evidence is needed before a conclusion is warranted.

There is little doubt, on the other hand, but that the liver is involved, tho there is some question whether this organ belongs to the endocrine system. In the light of our present knowledge of carbohydrate and fat metabolism, however, the processes that lead to ketosis appear to be more physiologic than pathologic in nature.[47] If true hepatic dysfunction occurs in ketosis of ruminants, it probably does not develop until late in the syndrome, when treatment with glucose or similar carbohydrate often fails to prevent death of affected animals.[107]

[a] The discussion on endocrine organs was prepared before Shaw[120a] published results of a study on the relation of the adrenal cortex to ketosis in the cow. Shaw concluded that the adrenals are probably not involved in ketosis of the bovine, but that cortical extract might nevertheless prove beneficial in treatment.



Liver of Hereford heifer affected with severe ketosis. Numerous vacuoles in the parenchyma indicate an abundance of lipoidal substance. Hematoxylin and eosin. (a)×90, and (b)×450. (Fig. 1)

Histopathology

The histopathology of ketosis in ruminants has been studied more thoroly in ewes than in cows. In fact, relatively few reports have been made of such studies in the bovine. A much lower mortality in ketosis of cows than in ketosis of ewes probably explains the scarcity of such observations. Furthermore, histopathologic studies of ketosis in cows have been limited largely to those organs which usually show gross changes, namely, the liver and kidneys.

Sjollema and Van Der Zande[128] examined the liver of a cow that had died of acetonemia 10 days after parturition. The liver was yellow and somewhat enlarged. Microscopic examination showed some fatty degeneration. Similar fatty degeneration was seen in the heart and kidneys. Fatty changes in the liver of a cow that died of ketosis were also observed by Roderick and Harshfield.[99] Such changes have also been reported by McIntosh,[78] who states, "Post-mortem examination of cows which die from the disease ketosis or acetonemia reveals a fatty liver. . . . " Morrill[114] made a careful histopathologic study of the liver of a pregnant beef heifer affected with severe ketosis and found a high content of lipoidal material (Fig. 1).

Additional comment on fatty changes in the liver and kidneys of ruminants affected with ketosis appears in the discussion of pregnancy disease of ewes, pages 445-447.

Symptoms

Ketosis in cows has been described many times during recent years. Sampson, Morrill, and Alberts[114] published a detailed report on spontaneous ketosis in a Hereford heifer during advanced pregnancy, and Kingman *et al.*[58] and Rainey[95] also call attention to the fact that cows in late pregnancy may develop clinical ketosis. Ketosis in the bovine is, however, primarily *postparturient.* Data collected by Henderson[51] on age, breed, and time of year in relation to incidence of ketosis in cattle are shown in Table 2. According to Messervy,[79] the incidence of ketosis of cows in the Island of Jersey is about the same thruout summer, autumn, and winter. And Schwab[116] states that acetonemia occurs at all seasons of the year in Wisconsin.

Certain striking manifestations have been mentioned in nearly all descriptions of bovine ketosis or acetonemia, but it cannot be said that all cows affected with ketosis show the same symptoms. Usually, however, if the affected cow is lactating there is (1) a marked decrease in milk production,[a] (2) increasing somnolence, and (3) rapid

[a] Occasionally a cow affected with ketosis continues to produce well, but in such cows the loss of condition is usually greater than normal in spite of high caloric intake.

TABLE 2. — RELATION OF AGE, BREED, AND MONTH OF YEAR TO PRESENCE OF KETOSIS (ACETONEMIA) IN COWS[a]

Relation of age

Calves born	Cows in each class	Cases of acetonemia	Approximate ratio	Calves born	Cows in each class	Cases of acetonemia	Approximate ratio
1	165	8	1:21	5	45	4	1:11
2	132	12	1:11	6	26	2	1:13
3	98	14	1: 7	7 or over	27	2	1:13
4	72	8	1: 9				

Relation of breed

	Holstein	Jersey	Guernsey	Ayrshire	Brown Swiss	Shorthorn
Number of parturitions	260	131	89	93	36	20
Cases of acetonemia	24	13	11	7	0	0
Approximate ratio (1:)	11	10	8	13	..	..

Relation of season

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Number of parturitions	85	61	58	27	25	19	33	41	50	71	66	75
Cases of acetonemia	8	7	14	5	1	2	2	2	2	3	3	6
Approximate ratio (1:)	10	8	4	5	25	9	16	20	25	23	22	12

[a] Data of Henderson slightly modified. Cornell Veterinarian **28**, 173-195 (1938).

emaciation.[128, 107] *A few cows are in an excited state, and such cases have frequently been erroneously diagnosed as rabies* (see pages 411 and 412). Cows affected with the nervous type of ketosis may push against a fence, wall, stanchion or other immovable objects. Often they walk on their "knees" and manifest other unusual movements. With some exceptions, affected cows have an irregular and often complete lack of appetite. Body temperature, respiratory and pulse rates are usually normal (except in cases of the nervous type). The feces are often hard, dry and covered with mucus, altho diarrhea is observed in a few cases. Atony of the rumen may or may not be present. The abdomen is often "tucked up" and the cow stands with the hind feet pushed forward under the body. In some cases scoliosis is a prominent symptom. The head is often carried in a lowered position and, if the cow is lying down, the head often rests in the flank as in milk fever. The eye is usually dull and lusterless (Fig. 2).

The dejected and listless attitude assumed by most cows affected with ketosis, together with the elimination of hard dry feces, probably accounts for Hupka's[56] classification of bovine ketosis into "digestive" and "nervous" types. Actually this classification is misleading. As

Severe uncomplicated ketosis (acetonemia) of nonnervous type in a high-producing dairy cow. This cow was in excellent condition at the time of calving. A marked loss of body weight occurred during the attack. The cow was very weak when these pictures were taken and died after treatment with chloral hydrate. See page 436 for further comment. (Fig. 2)

Sjollema and Van Der Zande[128] point out, even tho the symptoms "resemble those of indigestion . . . acetonemia causes changes in the composition of the urine which are different from those due to acute indigestion. In some cases a veterinarian made the diagnosis of acetonemia, but found he was mistaken when we declared the urine to indicate an acute indigestion." Also it is significant that the usual treatments for indigestion in cows are ordinarily not effective for ketosis. It would seem advisable, therefore, to discontinue the use of the term *digestive* and describe ketosis of cows as *nervous* and *non-nervous* types.

In addition to the symptoms that have been mentioned, many cows affected with ketosis show evidence of pica and an exaggerated desire for licking their bodies or nearby objects. (For further comment on symptoms see clinical discussions by Udall[137] and by Hutyra, Marek, and Manninger.[57])

Finally, the cow affected with severe ketosis may be unable to rise, somnolence is increased and is frequently followed by coma and death. An interpretation of the symptoms and an explanation of the histopathology and death in ketosis of cows are purposely omitted here. These topics are considered from a comparative viewpoint in the discussion of ketosis in ewes, page 450.

Diagnosis

In discussing the diagnosis of ketosis in cows, Sampson[105] has stated:

> The writer does not believe an accurate differential diagnosis can be made without recourse to a test of the urine for the presence of ketone bodies. In many instances it is difficult to determine whether a cow is affected with atony of the rumen, metritis, ketosis, or a combination of all three without checking the urine for ketones. [Indigestion, metritis, and ketosis may occur simultaneously or independently.] Even a light purple color, if the test is made with undiluted urine, should not be dismissed without some possible significance because the cow may be in the very early stage of an attack. Some veterinarians responsible for the health of individual dairy herds have adopted the practice of testing the urine of all milk cows at frequent intervals during lactation. The urine test, tho a useful tool in diagnosis, is not infallible because it does not detect such complicating diseases as metritis, indigestion, traumatic gastritis, or milk fever. The careful clinician will not overlook these possibilities in arriving at a diagnosis.

A number of writers[29, 32, 14] have been disturbed because (1) the urine of apparently healthy cows may give a positive reaction to Rotheras' test (or a modification of this test) for acetoacetic acid and acetone, and (2) a positive test fails to reveal the exact intensity of ketonuria and ketonemia. Experience in using the Ross modification of Rotheras' method on a large number of samples of urine is helpful in interpreting results. For example, if an appreciable amount of ketone bodies is present and continues to be eliminated in the urine, there is an excellent chance that definite symptoms will develop and furthermore that even when mild ketonuria and ketonemia are present, careful observation may reveal either a decrease in milk flow, an irregular appetite, or excessive loss of body weight. *If metritis, indigestion, and other conditions which may affect the appetite are absent, it seems highly probable that a positive test for ketone bodies in urine of lactating cows should be looked upon as a danger signal — a warning that the animal is metabolizing fat at a faster rate than is desirable and that an increase in consumption of readily available carbohydrate is indicated.* Because of this view the author does not recommend, as Sjollema[127] and Roepke[102] have suggested, that urine be diluted 1 to 10 before a test is made for ketone bodies. A test made of diluted urine, however, takes little additional time and may be helpful in differential diagnosis.

A detection of the odor of acetone in the expired air of affected cows is helpful in establishing a diagnosis of ketosis, but is not as reliable as the urine test. If facilities are available, it is advisable to

make quantitative determinations of blood sugar and calcium and blood and urine ketone bodies as these determinations are helpful in clinching a diagnosis. A qualitative test[a] of the milk for ketone substances may also be advisable.[26]

Treatment

The classic studies of Mann and his associates[73, 74] on the physiology of the liver have shown that intravenous administration of glucose is the most effective method of alleviating hypoglycemia. The effectiveness of carbohydrate therapy for hypoglycemia and ketonemia in ketosis of ruminants has been so thoroly demonstrated clinically as well as experimentally that there can hardly be any doubt as to its specificity. [132, 107, 102, 123, 119] *In fact, carbohydrate therapy is so specific for acetonemia of cows that unless the condition is complicated by milk fever or some other disease, there is little to be gained from any other treatment.* If milk fever is a complication, calcium gluconate as well as glucose is indicated.[35] As it is often difficult to determine whether milk fever is involved unless a chemical analysis is made for blood calcium, the administration of both glucose and calcium gluconate may be justified, particularly when ketosis develops shortly before or soon after parturition. Calcium gluconate, however, especially when given intravenously, must be administered with much greater caution than glucose. If ketosis is associated with metritis, indigestion, or other disorders, appropriate treatment for these conditions should supplement carbohydrate therapy.

Sterile glucose solution seems to be admirably suited for intravenous administration to ruminants. Ordinary 50 percent dextrose solution or solutions containing both dextrose and calcium gluconate are widely used by veterinarians. It is often advantageous to supplement intravenous administration of dextrose by drenching or feeding the cow corn sugar or a feeding grade of molasses. Three to six pounds may be given for several days, depending on the severity of the ketosis and the response to treatment. Udall's[137] textbook contains additional information on carbohydrate therapy for ketosis of cows.

The first report on the use of chloral hydrate in treating acetonemia appears to be that of Robellet (see page 411). Still a popular treatment with some veterinarians, it has its greatest usefulness in treating the nervous type of acetonemia.[98] According to Udall,[137] it is often used in

[a] Roepke, in a conversation with the author in December, 1947, recommended the following test: To 5 cc. of milk add approximately 2.5 grams of 2-percent nitroprusside mixture (2 grams of sodium nitroprusside plus 98 grams of ammonium sulfate). Shake well and add 1 cc. of concentrated ammonium hydroxide.

30-gram doses given once or twice daily. It is a dangerous form of therapy when ketosis is complicated by milk fever,[35] and even in uncomplicated acetonemia if the cow is weak or emaciated.[107, 105] The cow shown in Fig. 2 was affected with severe ketosis. Chemical analysis of the blood revealed the following data: calcium 10.3 mg. percent, sugar 27.12 mg. percent, total ketone bodies as acetone 132.31 mg. percent. The veterinarian who treated this case preferred chloral hydrate to glucose and, despite the fact that the dose given (approximately 30 grams) was not excessive, the cow failed to revive from the stupor produced by the drug. It should be mentioned that this cow was very weak and was affected with the nonnervous type of ketosis.

Sodium bicarbonate and insulin have been recommended,[127] but it is doubtful if either is beneficial. Haldane[46] has shown that administration of sodium bicarbonate may cause ketonemia presumably by interfering with normal oxidation of sugar in the body. On the other hand, MacKay, Wick, Carne, and Barnum[71a] believe the ketogenic effect of alkalosis is caused by a decrease in protein catabolism with a consequent reduction in glucose formation. Insulin is not indicated because, as previously mentioned on pages 417, 429, ketosis in ruminants is not associated with diabetes mellitus. In fact, it is probably contraindicated, for, as Soskin[130] points out, an excess of insulin in the body may increase glycogen in the muscle at the expense of glycogen in the liver. By causing sugar in the blood to be deposited in muscle but not in liver tissue, excess insulin apparently removes glycogen from the liver to maintain the normal concentration of glucose in the blood. This is the reverse of that which is desired; namely, that the glycogen content of the liver be increased.

Vitamin B_1[16, 22] and vitamin A[71, 90, 133] also have been recommended in treating ketosis of ruminants but, as stated in the discussion of etiology on page 428, it is difficult to explain the rationale of such treatments. Vitamins B_1 and A, however, should be used, if it can be proved that these compounds are distinctly beneficial. Miller[81] has suggested that if vitamin A is beneficial in the treatment of acetonemia, the action may be the result of increased hepatic glycogen. According to Miller, a large excess of vitamin A may be responsible for increasing the glycogen content of the liver.

Much more critical evidence than is now available is needed before a final decision can be reached as to the true value of either vitamin B_1 or A therapy for ketosis. At the present time, observations reported by Forbes,[38] Shaw, Matterson, Surgenor, and Hourigan,[121] and Shaw[119] cast serious doubt on the beneficial effects claimed for vitamin B_1 (as well as other members of the B-complex) and A in treating acetonemia

of cows. Forbes states that the favorable results obtained by Carlström with thiamin hydrochloride could not be repeated by him; and Shaw *et al.*, and Hayden, Fincher, Roberts, Gibbons, and Danks[48] failed to confirm the results reported by Patton[90, 91, 92] with vitamin A. Shaw and associates reported:

Nine cows with severe ketosis as shown by ketonemia, hypoglycemia and lack of appetite had an average blood-plasma carotene level of 321.8 micrograms per 100 ml. of plasma (range 131 to 768). Vitamin A was determined on seven of these animals and was found to average 24 micrograms per 100 ml. of plasma (range 14.4 to 33.6). The oral administration of from one to four million units of vitamin A per day for as long as three weeks was completely ineffective in improving the appetite, or alleviating the hypoglycemia and ketonemia.

Hayden and associates[48] concluded:

It is not unreasonable to assume that vitamin A deficiency would be overcome by proper vitamin A therapy. We conclude that none of the cases of ketosis we have so treated have been due to vitamin A deficiency. The vitamin may have been of some help in some of these cases but it has in no sense been a specific or needed therapy.

On the other hand, Krill (*personal communication*) states that vitamin A therapy has been beneficial in some cases of ketosis in cows that did not respond to "the usual line of treatment for acetonemia." As it has been shown that large doses of *some* vitamin A concentrates produce toxic effects in rats, the possibility of exceedingly large, repeated doses of certain forms of vitamin A products having a deleterious effect in cows cannot be ignored.[104]

Prevention

It seems evident that at least two conditions are essential for the prevention of ketosis in high-producing cows: (1) a liberal ration made up of palatable nutritious feeds must be provided[a] and (2) the cow must have a good appetite. These two conditions also have been shown to be of paramount importance for the prevention of ketosis or pregnancy disease of ewes[33, 107, 45, 6, 125, 140, 54, 66] (see pages 440, 441 and 454).

Sampson[105] and Forbes[38] have called attention to the importance of several influences which may affect the appetite of cows. Among these may be mentioned such abnormal conditions as metritis, indigestion, or any other illness and, according to Nevens[86] and Blaxter,[9] even such physiological factors as breed and individual animal likes and dislikes

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[a] Rations for dairy cattle are given in Illinois Circular 502, "Feeding the Dairy Herd."

for certain feeds. Sampson and Forbes also believe that the common practice of sharply reducing the feed intake for one week or longer after parturition, may contribute to an attack of acetonemia in some high-producing cows. Good judgment on the part of the herdsman is needed to determine whether the caloric intake should be reduced and how rapidly it should be restored or increased during this period. As mentioned elsewhere (page 423), the incidence of ketosis presumably is significantly lower when cows have access to luxuriant pasture than when they are stall-fed.[29]

KETOSIS (PREGNANCY DISEASE) IN SHEEP

As stated on page 420, a significant ketosis in cattle and sheep is apparently restricted largely to females during pregnancy and lactation. Furthermore, in ewes ketosis is primarily *preparturient*, whereas in cows it is primarily *postparturient*.

At least 19 names have been given to ketosis of sheep, but the fact that it occurs mainly during gestation probably explains why the name *pregnancy disease* has been adopted by most writers. Groenewald and associates[45] mention the following list of names to illustrate the numerous terms ketosis of sheep has acquired:

acute parenchymatous hepatitis, acetonemia, acute partum eclampsia, acidosis, domsiekte, ewe-paralysis, eclampsia, fatty infiltration of the liver, ketonaemia, ketosis, lambing paralysis, lambing sickness, ophaalzieckte, pregnancy disease, preparturient paralysis, parturient paresis, pregnancy toxaemia, parturient fever, sleepy sickness, stercoraemia, tremblings, twin tremblings, uterine acetonaemia, and white liver.

In 1933 Sampson, Gonzaga, and Hayden[110] reported:

Data we have thus far accumulated indicate that there is a definite ketosis (acetonemia) in cases of so-called pregnancy disease in ewes. The blood and urine picture resembles very closely that found in the blood and urine from cows with typical cases of acetonemia. . . . In all probability the etiological factors, whatever they may be, are the same in both the acetonemia seen in cows and the acetonemia met with in pregnancy disease of ewes.

Since 1933 more and more evidence has accumulated to support the above point of view. For example, Groenewald and associates,[45] in a report published in 1941 of results obtained in a critical study of pregnancy disease or domsiekte of ewes in South Africa, make the following statements:

As it is extremely likely that there are at least common factors in the "pregnancy disease" of different species, short reference will be made to the literature on this category of conditions. The parallel between preg-

nancy disease in sheep and acetonaemia in the cow would appear to be especially close. This is pointed out by Sampson *et al.* (1933) and by Webster (1935). The latter author states that no similar condition has been seen in goats, pigs or horses. Hudson (1931) describes an acetonaemia, hypoglycaemia, and nervous symptoms in cows shortly after calving, all of which closely correspond to the changes seen in domsiekte. It is quite conceivable that the drainage of lactation in the cow would take the place of that of gestation in the sheep in the chain of aetiological factors. Furthermore it must be remembered that cases of domsiekte have been reported after lambing.

The parallel with Milk Fever in the cow does not appear to be so close, especially in that the classical calcium treatment for Milk Fever does not appear to assist in domsiekte . . . and also that the blood calcium during domsiekte is reported to be normal.

Numerous References to Ketosis in Ewes

The imposing list of names (page 438) given to ketosis, or pregnancy disease, of sheep suggests that it has been described many times. Groenewald and coworkers[45] state that apparently one of the first definite references to pregnancy disease of the ewe was that of Steele, who in 1890 described a disease which he called "parturient fever in sheep." Henning, cited by Groenewald and associates, stated in 1932 that domsiekte of ewes "has been known in the Cape Colony for more than 50 years." Roderick and Harshfield,[99] in the excellent report published by them in 1932 on studies of pregnancy disease in North Dakota, state that observations reported by Gilruth of New Zealand in 1909 probably were among the earliest discussions on the problem.

Thus despite the fact that until comparatively recent years very little information was available with reference to etiology, pathologic physiology, and prevention of ketosis of ewes, the syndrome was probably recognized as a specific disease of sheep as early as 1890 or even perhaps at a much earlier date in the 1800's.

Economic Importance

General agreement among investigators who have studied ketosis of sheep indicates that a mortality of 1 to 25 percent may be expected when pregnancy disease makes its appearance in a flock of breeding ewes. Occasionally the losses are much higher than 25 percent. For example: Dimock, Healy, and Hull[27] of Kentucky reported a 60 percent loss in one flock of 100 ewes. Similar heavy losses from pregnancy disease have been reported in such widely separated regions as South Africa[45] and Australia.[52] In 1940 Elder and Uren[33] stated:

One of the chief losses suffered by the sheep industry in Missouri is that

due to pregnancy disease, which causes its greatest trouble during the months of January and February. This disease occurs in all parts of Missouri, and in some cases the losses have been very heavy.

The economic loss from pregnancy disease is especially severe because about 90 percent of ewes affected carry more than one fetus;[99] hence the loss of lambs is in itself no small item. The total loss continues to be heavy altho a steady decrease may be expected as more and more flock owners adopt feeding and management practices which have proved effective in preventing the disease (see page 454).

Incidence

Roderick and Harshfield[99] and Groenewald *et al.*[45] state that the occurrence of pregnancy disease seems to be world-wide; but according to the latter investigators the main countries where it occurs are the United States, Australia, Great Britain, New Zealand, South Africa, Canada, Holland, France, Germany, and Austria.

In the United States it is apparently observed in all states and in all breeds of sheep. Marsh[75] states that it is observed in small flocks but is apparently not common in range flocks. Roderick and Harshfield report that it has been observed in "western" ewes shipped to North Dakota. The author has observed several severe outbreaks of pregnancy disease in large flocks composed of "western" ewes in Illinois. Cross (*personal communication*) writes from Colorado:

> We see this condition in milk cows occasionally, but it is most commonly observed by us in ewes. This condition is especially prevalent on the western slope of Colorado where large numbers of range ewes are run. These ewes are wintered on the desert and, as spring approaches, feed becomes progressively short and the ewes are losing weight at the time when they are approaching termination of pregnancy. This condition is further aggravated by snow storms which from time to time cover the available forage.
>
> In the spring, just before the ewes are to lamb, they are moved from the desert to the high mountain areas. This journey is usually made by train, but in some instances they are driven overland. Upon arriving at their destination in the high mountain areas, large numbers of these ewes suffer from ketosis, and the loss is often alarming.
>
> We have been able to solve this problem very satisfactorily by feeding the ewes a sufficient amount of concentrate of either corn or cotton cake while on the desert so that they are actually gaining weight to some degree as the end of pregnancy approaches. We have also found that it is necessary to provide abundant feed for the ewes just prior to and during their journey to the mountains.

Published reports from such widely separated states as New York and California indicate that ketosis, or pregnancy disease, of ewes probably occurs in all sections of the Americas where sheep are raised.

Etiology Believed to Be Established

Enough critical evidence is available to warrant the definite statement that the etiology of ketosis, or pregnancy disease, in ewes is now reasonably well established. No useful purpose will be served, therefore, by reviewing the theories which have been put forth from time to time as to the cause of the disease. An excellent recapitulation of these theories is given by Groenewald and associates[45] who concluded:

Many of the suggested causes such as mineral deficiency, toxic absorption from the uterus and lack of exercise, can be discarded. Age, overfatness and changes in the climatic or feeding conditions can be looked upon as predisposing or indirect causes. The disease is essentially a disturbance of metabolism, especially with regard to the carbohydrates, and this is usually manifested by a loss of body weight. Pregnancy is a powerful predisposing cause and acts through the increased drainage on the maternal system.

Results of well-planned experimental studies by Fraser, Godden, Snook, and Thomson,[40, 41] and Groenewald, Graf, Bekker, Malan, and Clark[45] confirmed the earlier observations of Roderick and Harshfield,[99] Hopkirk,[52] and Roderick, Harshfield, and Hawn[100] that typical ketosis, or pregnancy disease, occurs in ewes fed adequate as well as inadequate rations. Groenewald *et al.* also helped clarify the problem by showing that it was not a lack of exercise *per se* which is responsible for the development of pregnancy disease in well-nourished ewes but rather the sudden reduction in the amount of nutrients consumed by these ewes. Sudden changes in weather, e.g., a heavy snow fall and extremely cold weather, and sudden changes in feed are believed to have an adverse effect on the appetite of pregnant ewes. At any rate, Roderick *et al.*, Hopkirk, Fraser *et al.*, and Groenewald *et al.* have definitely demonstrated that a sharp reduction in an adequate ration fed to ewes in advanced pregnancy causes ketosis and symptoms indistinguishable from those found in natural pregnancy disease. *In all countries where pregnancy disease has been described, however, the great majority of cases occur in ewes that are underfed during pregnancy, especially during the last one-third of the gestation period.* Inasmuch as there is little evidence that fat can be changed to carbohydrate in the body (except the glycerol fraction of the fat molecule)[47] the fundamental cause would seem to be an inadequate consumption of readily available carbohydrate or potential carbohydrate, such as protein. (See also page 423.)

Ketonemia and hypoglycemia are often as intense in ketosis of ewes as of cows. Comparative data published by Sampson and Hayden[113] reveal that ketonemia and hypoglycemia often are as severe in ketosis, or pregnancy disease, of the ewe as in ketosis, or acetonemia,

TABLE 3. — TOTAL KETONE BODIES AND SUGAR IN BLOOD OF HEALTHY EWES IN ADVANCED PREGNANCY, AND OF EWES AFFECTED WITH EXPERIMENTAL AND CLINICAL KETOSIS (PREGNANCY DISEASE)

(Ketone bodies expressed as acetone; sugar determined by Shaffer, Hartmann, and Somogyi[93] method)

Healthy ewes in advanced pregnancy			Experimental ketosis			Spontaneous ketosis		
Ewe	Ketone bodies	Sugar	Ewe	Ketone bodies	Sugar	Ewe	Ketone bodies	Sugar
	mg/100 ml	mg/100 ml		mg/100 ml	mg/100 ml		mg/100 ml	mg/100 ml
1923	4.78	42.94	1737	23.81	14.69	1	67.21	No detn.
1707	.75	38.42	1933	27.77	53.11	2	96.22	21.47
1895	1.12	45.20	37	40.92	22.60	3	19.47	31.64
1852	1.86	42.94	1801	32.74	24.86	4	35.96	23.73
1841	5.15	42.94	1868	16.99	31.64	5	47.24	16.95
1983	1.98	43.00	1901	18.85	24.86	6	25.42	40.68
1757	1.24	51.98	1954	20.58	21.47	7	15.25	50.85
1918	.99	42.94	1834	21.82	15.82	8	29.76	18.08
1849	.50	39.55	....	.....	.....	9	36.45	18.08
Average	2.04	43.32	Average	25.43	26.13	Average	41.44	27.68

of the cow (see also Tables 1 and 3). The author and his coworkers at the Illinois Agricultural Experiment Station have confirmed the observations of Hopkirk, of Roderick, Harshfield, and Hawn, of Fraser *et al.,* and Groenewald and associates that severe ketonemia and hypoglycemia can be readily produced in ewes during late pregnancy either by fasting or by rations low in caloric value. Data obtained in fasting experiments at the Illinois Station are shown in Table 3. See also Fig. 3. Symptoms of experimental ketosis are ordinarily indistinguishable from symptoms observed in natural ketosis in the ewe. Normal values for total ketone bodies and sugar of blood of healthy ewes and ewes affected with spontaneous ketosis, also shown in Table 3, compare favorably with other published data.[99, 110, 106, 15]

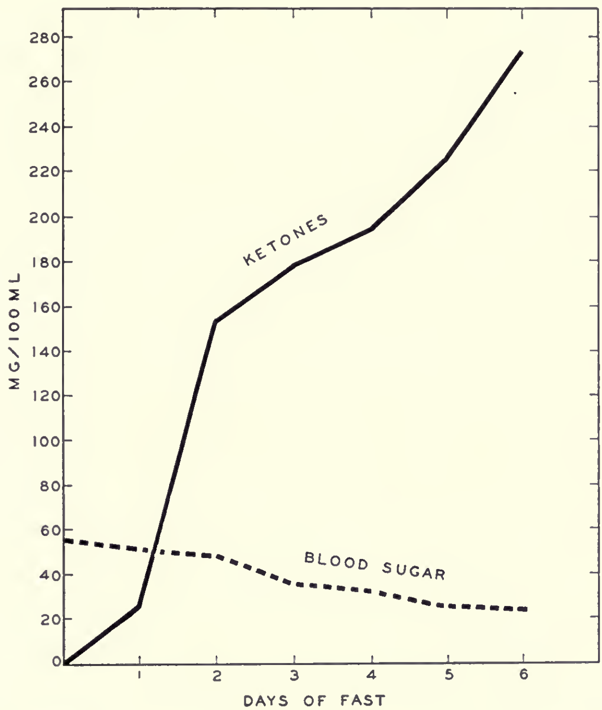
As is true in acetonemia of cows, the alkali reserve or carbon dioxide combining power of the blood may be definitely lower than normal in ewes affected with pregnancy disease.[110] Acidosis, as judged by the alkali reserve, however, is apparently of less significance in ketosis of cows and ewes than in ketosis of humans.[107, 29, 32]

Also, as in acetonemia in the cow, such constituents as calcium,[a] inorganic phosphorus, magnesium, chlorides, iron and hemoglobin of the blood usually show no abnormal changes in ketosis of the

[a] According to Dr. A. K. Sutherland (*personal communication*), a disease characterized by hypocalcemia occurs in sheep in Australia. It usually develops in ewes during the early part of lactation, but may also occur in late pregnancy.

ewe.[112, 45, 138, 139] But contrary to what has been reported in ketosis of the cow, there does not appear to be a cholesteremia in ketosis of the ewe.[45]

In the early stages of pregnancy disease, values for nonprotein nitrogen of the blood are ordinarily found to be in the normal range. In the late stages of the disease, however, high nonprotein nitrogen values are the rule. Sampson *et al.*[110] have stated that high concentrations of nonprotein nitrogen are probably associated with oliguria and



Relation between concentration of blood sugar and blood ketones. Graph shows average values in blood of four fasting ewes in advanced pregnancy. Total ketone bodies are expressed as acetone. (Fig. 3)

in some cases anuria and are probably indicative of uremia. Groenewald and associates[45] have also reported high values for nonprotein nitrogen in blood of ewes affected with ketosis during the advanced stages but, as suggested by Fraser *et al.*,[40] are inclined to attribute this marked rise to increased catabolism of protein. Nevertheless Groenewald and associates call attention to two ewes in which a daily elimina-

tion of urine was only 86 ml. and 20 ml. respectively. It may be that both increased protein catabolism and, in some cases at least, oliguria and anuria contribute to the rise in the nonprotein nitrogen of blood. The author's opinion is that blood pressure is often so low in advanced pregnancy disease that the rate of urine formation is decidedly subnormal. Further study is therefore needed to determine the cause or causes and the significance of the increase in nonprotein nitrogen of blood in severe ketosis of sheep.

Changes in urine. The changes in urine in ketosis of ewes are similar to changes found in urine of cows affected with acetonemia. For example, there is a pronounced ketonuria. The concentration of ketone bodies in urine of the ewe suffering from pregnancy disease often is as great as it is in urine of the cow suffering from acetonemia. Sampson, Gonzaga, and Hayden[110] found 735.5 mg. of total ketone bodies as acetone per 100 ml., or roughly 7 grams per liter of urine in one case of mild pregnancy disease. The author has unpublished data showing that urine of ewes affected with severe ketosis may contain as much as 14 grams of total ketone bodies per liter. These values are unusually high for urine of ewes affected with pregnancy disease, but they compare favorably with maximum values of 10 to 13 grams of ketone bodies per kilogram of urine reported by Sjollema and Van Der Zande[128] in acetonemia of the cow.

The content of ammonia also is ordinarily greatly increased in urine of ewes affected with pregnancy disease. The explanation for such a high content of ammonia is probably the same as that for the marked increase of ammonia usually found in urine of cows affected with acetonemia (see page 427). Apparently no extensive data are available with reference to the content of calcium and other constituents in urine in ketosis of the ewe. Urine of cows and ewes affected with ketosis is often acid to litmus, whereas normal urine of ruminants is alkaline.[28] In uncomplicated ketosis of the cow and ewe there may be an albuminuria which ordinarily disappears when the animal recovers. Tests for sugar in the urine of either cows or ewes affected with ketosis are invariably negative unless concentrated solutions of sugar have been administered prior to such tests. Lactose may be found in urine of cows, however, near the onset of lactation.[28]

Gross and Microscopic Pathology

As mentioned on page 431, the histopathology of ketosis in ruminants has been studied more thoroly in the ewe than in the cow. Investigators agree apparently that pathologic changes are limited primarily

to the liver and kidneys. Roderick and Harshfield,[99] Dimock, Healy, and Hull,[27] and Clark,[45] for example, have given excellent descriptions of these changes. Roderick and Harshfield, in describing the changes in the liver, state:

The liver often presents a striking appearance on necropsy. There is a marked alteration in the color from the reddish brown of a normal animal, so that it assumes a tawny yellow, clay, or putty color. It is very friable and the cooked appearance is evidence of the extreme degree of parenchymatous injury. . . . The livers of a large number of our cases, about 50 of them, have been examined histologically and a remarkable uniformity in the character of the microscopic changes is seen. The differences are largely a matter of degree and extent of the injury. The cytoplasm of the cells, rather than the nuclei, is involved. There seems to be little actual necrosis, for the nuclei are ordinarily intact although pressed to one side of the cell by the fat globules. Vacuolation of the cytoplasm is common while the cells in many areas have a granular appearance. The use of a fat stain (Oil-Red-O) clearly shows the extensive degree of injury and the enormous extent of the retrograde fatty changes. This condition of the liver in ewes in winter and spring is really pathognomonic for pregnancy disease. It is doubtful if any other disease of livestock involves such an extensive degree of fatty change in the liver. A study of the references given under human toxemias of pregnancy reveals that the pathology of that disease shows a remarkable similarity to the changes in the livers in these sheep.

The intense fatty infiltration of the liver which is characteristically found in ketosis, or pregnancy disease, of the ewe is shown in Figs. 4 and 5.

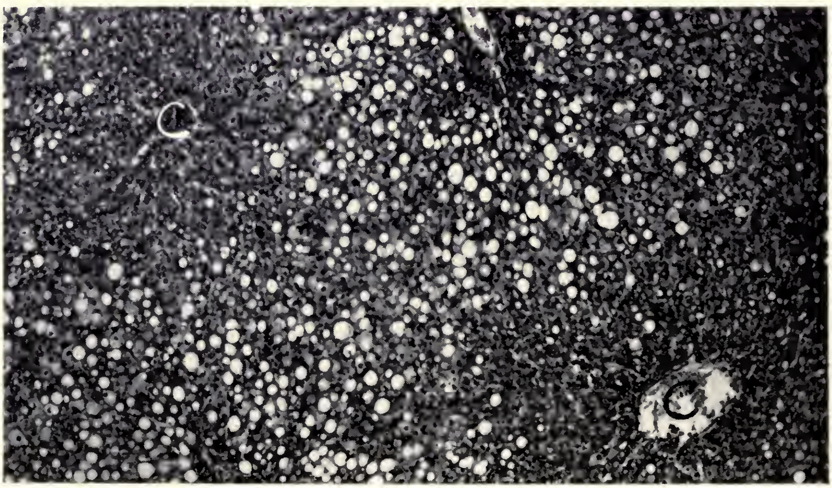
With respect to the pathology of the kidneys in ketosis of the ewe, Roderick and Harshfield state:

The kidneys in pregnancy disease likewise show a remarkable uniformity in the character of the lesions which are present. Previous comment was made on the lack of gross changes in the kidneys. There seems to be little recognizable change in the glomeruli, but there is apparently some swelling of the epithelium lining the convoluted tubules. Casts have not been encountered in our kidney sections. The most significant finding is the presence of fat droplets in the epithelial cells of the ascending and descending limbs of Henle's loops at the edge of the cortex. More advanced cases show a greater degree of involvement. . . . This characteristic lesion of the disease has not been observed in normal sheep. No trace of any cellular infiltration has been observed, so it is no doubt a toxic injury rather than one of inflammation.

Clark agrees with Roderick and Harshfield that marked fatty changes are present in the liver and kidneys of ewes affected with ketosis, or pregnancy disease, but he does not seem to attach the same significance to these changes. In illustration, Clark states:

Although this fatty infiltration of the liver is the most apparent change seen in Domsiekte (pregnancy disease) and is probably constantly present,

Liver from sheep with advanced ketosis (pregnancy disease). Yellow discoloration was widespread. Note fine mottling, which denotes variation in distribution of fatty changes within the lobules. (Fig. 4)



Section from liver shown in Fig. 4. Note tendency toward more marked concentration of fat in peripheral parts of the lobules. C = central vein. Hematoxylin-eosin. × 170. (Fig. 5)

it cannot, of course, be considered specific. The degree of fatty infiltration does not show any relation to the severity of the symptoms. In fact sheep that showed no symptoms presented fatty infiltration of the liver to the same extent as those that died in coma. Further, the normal pregnant sheep from group 1 which was slaughtered for the collection of comparative material showed a fatty infiltration equal to many of the Domsiekte cases.

With respect to the kidneys in pregnancy disease, Clark summarizes his observations in these words:

It will be seen that the kidney changes constitute a nephrosis in the generally accepted meaning of that term, and these findings confirm those of Roderick and Harshfield (1932) in all respects except that more advanced lesions were found, consisting of the formation of casts and the presence of glomerular degeneration.

The observations reported by Clark of the presence of casts and the evidence of glomerular degeneration in the kidneys seem to be in accord with the findings of Dimock, Healy, and Hull. These authors reported the results of observations made in autopsies of 106 ewes that were "dead from acidosis or that were killed in an advanced stage of the disease."

Dimock *et al.* state:

Microscopical examination of kidneys from different ewes revealed a variety of changes varying from a simple granular degeneration, most pronounced in the convoluted tubes, to complete disintegration of the cytoplasm of the cells lining the tubules. . . . The glomeruli were not, as a rule, appreciably abnormal except that occasionally an individual glomerulus showed congestion and hemorrhage, and in a few glomeruli a granular exudate was observed within the capsule but separated from the cellular structure of the glomerulus.

It seems evident that complete agreement has not been reached among pathologists as to the extent and significance of changes in the liver and kidneys, particularly in the liver, of ewes that succumb to ketosis and that further study is needed.

Clark mentions the interesting observation that "in all cases the adrenals were enlarged and exhibited marked degenerative changes. The organ was extremely friable, it often being almost impossible to extract it whole from the surrounding fat. On section the cortex was flabby and yellow." Apparently these abnormal changes in the adrenals have not been observed by others. Clark sums up his observations as follows:

The post-mortem findings in these eight cases of undoubted Domsiekte were: General cyanosis, fat necrosis especially of the perirenal and omental fat. Fatty changes of the liver, renal cortex and adrenal cortex and atrophy of the lymph glands.

Severe ketosis (pregnancy disease) in a ewe. (a) While the ewe was still able to stand and walk; (b) during late stage, several hours before death. (Fig. 6)

According to Clark, changes that occur in the lymph glands are probably responsible for a decrease in the number of lymphocytes found in the blood.

The investigators who have been mentioned in the discussion on gross and microscopic pathology of ketosis of the ewe appear to hold the opinion that no significant changes are found in other organs and tissues of the body exclusive of those described in the preceding paragraphs.

Symptoms

In general, most of the symptoms of uncomplicated ketosis in the ewe closely resemble the symptoms associated with the nonnervous type of ketosis in the cow. Trembling, twitching or shaking movements of the head are often observed in ketosis of the ewe but extreme excitability which sometimes characterizes the nervous type of ketosis in cattle apparently does not occur in sheep. In the following discussion on symptoms any reference to ketosis in the cow refers to the nonnervous type of acetonemia.

As in the cow, one of the characteristic symptoms of ketosis in the ewe is lack of appetite. Also, as in the cow, the feces are often covered with mucus and flecked with blood. The rate of respiration may be rapid in the early stage. The rapid breathing has sometimes led to the error of diagnosing pregnancy disease as hemorrhagic septicemia. The heart beat and pulse are often weak and almost imperceptible. Usually no significant change occurs in body temperature. Other symptoms often observed are grinding of the teeth and blindness. These symptoms are apparently less common in ketosis of the cow than in ketosis of the ewe.

The early stages of ketosis in the ewe are characterized by increasing somnolence or listlessness. The affected ewe is reluctant to rise and often moves with an unsteady gait. Ewes affected with ketosis are usually in advanced pregnancy and any evidence of "sluggishness" at this time may be erroneously attributed to pregnancy. Actually a healthy ewe, even in late pregnancy, has no difficulty in getting up and can walk and run with surprising ease. When the ewe is standing, the head is frequently held in a lowered position, as is often observed in ketosis of the cow (Fig. 6). Sometimes the head and neck are bent far backward. This position is often accompanied by twitching or shaking movements of the head. The syndrome rapidly becomes more acute, the ewe is unable to rise and passes into a deep stupor. Death usually occurs quietly with no evidence of struggling.

Cause of Death in Ketosis in Ruminants

Sampson, Morrill, and Alberts[114] have stated that if ketosis occurred in pregnant cows as often as it does in pregnant ewes, the rate of mortality might be expected to be as high among cows as among ewes. The burden of pregnancy is undoubtedly an added hazard and can be looked upon not only as a predisposing cause of ketosis but also as an indirect cause of high mortality of affected ewes.

It is evident also from what has been said concerning the significance of the rise in nonprotein nitrogen of the blood in advanced pregnancy disease that the immediate cause of death in ketosis of the ruminant, particularly in ketosis of the ewe, is still doubtful. That uremia may be an important contributing factor can hardly be questioned because, as Roderick and Harshfield,[99] Dimock *et al.*,[27] and Clark[45] have shown, definite changes occur in the kidneys. The true significance of these changes remains to be determined.

The author believes the views expressed by Hupka and Roepke (page 419) with reference to the significance of hypoglycemia in ketosis of the cow are of even greater importance in ketosis of the ewe. Roderick and Harshfield, and Sampson and Hayden, and others have clearly demonstrated that as the syndrome of pregnancy disease grows more acute, hypoglycemia also is likely to become more pronounced. Hyperglycemia may, however, be found in the terminal stage,[45] but it should be recalled that fluctuations in the concentration of blood sugar are not uncommon during a state of hypoglycemia. In illustration Bodansky and Bodansky[11] state:

> What is so generally overlooked is that the blood sugar value determined at any given point in an hypoglycemic seizure may have no relation whatever to the symptoms at the moment. Under conditions of instability or of disturbed homeostasis, the blood sugar may change almost from minute to minute. Thus, the concentration of blood sugar obtained during an attack is probably quite different from the concentration at the onset of the seizure, reflecting in all probability the resultant effect of the primary factor and of the compensatory mechanisms brought into play by the falling blood sugar.

It seems logical to believe that a rise in blood sugar in the late stage of pregnancy disease could be explained on this basis. As Riggs and Griffith,[96] Baker,[3] and Sherrill and MacKay[124] have shown, prolonged hypoglycemia causes permanent functional damage to the brain. Pathologic changes in the brain caused by hypoglycemia are not readily detectable, and this fact might account for the failure of Roderick and Harshfield and of Clark to find evidence of injury to this organ. Clark[45] states:

No visible lesions were discovered in the brain either macroscopically or microscopically. The microscopical study was, however, only carried out on Helle's and Formalin fixed material under the routine stains. It is admitted that more detailed cytological studies are necessary before any definite statement can be made.

Altho Roderick and Harshfield were apparently successful in demonstrating some degree of dysfunction of the liver in pregnancy disease, additional study is needed, especially with respect to the glycogen-storing function of the organ. There is also a need for careful study of the ability of the ewe to utilize carbohydrate in the advanced stage of ketosis. As is evident from the discussion on histopathology, the significance of the enormous amount of fat usually present in the liver in ketosis of the ewe is not well understood. The presence of this large amount of fat in the liver of cows and ewes affected with ketosis is in all probability the result of carbohydrate deficiency and the subsequent transfer of depot fat to the hepatic tissue. More work is needed on the probable deleterious effects of the ketone bodies, particularly of the acetoacetic acid fraction.

It must be admitted that at the present time the immediate cause of death in ketosis of ewes and cows is not definitely known. Further investigation may reveal that no single cause is responsible but rather that a combination of causes, including such influences as a disturbed carbohydrate-fat metabolism in the liver, possibly a decreased ability to utilize carbohydrate, functional damage to the central nervous system, and impaired function of the kidneys, is involved. To this must be added toxemia whenever the fetus dies *in utero*. These cases are not common because the lambs (and apparently calves also) are usually found alive even in the advanced stage of ketosis or pregnancy disease in ruminants.

Diagnosis

The author agrees with Roderick and Harshfield[99] that: "The occurrence alone of several losses in a flock of ewes in advanced pregnancy is a sufficient basis for suspecting the disease" (ketosis, or pregnancy disease). If the ewe shows the symptoms which have been enumerated and a positive test is obtained for ketone bodies in the urine, a diagnosis of ketosis is usually warranted.

If, in addition to the symptoms that have been mentioned, circling movements are observed, there is a good chance that the ewe is affected with listerellosis as well as ketosis. If the urine is free from ketone bodies and circling movements are a prominent symptom, the chances are that the ewe is affected only with listerellosis. It is also helpful in making a differential diagnosis if the history indicates that

losses have occurred in nonpregnant ewes, or in lambs, wethers, or rams. For more detailed discussions on the symptoms and pathology of listerellosis in sheep, see Olafson[89] and Graham *et al.*[44]

The author has mentioned elsewhere (page 420) that on the basis of his observations he does not believe a significant spontaneous ketosis occurs in lambs, wethers, rams, and nonpregnant ewes. Groenewald *et al.*[45] showed that moderate ketonemia and ketonuria could be produced in nonpregnant ewes after a prolonged fast. That this is a natural occurrence, however, seems a remote possibility. Lambs, wethers, and rams appear to be as susceptible to listerellosis as ewes; hence if losses have occurred in these classes of sheep, ketosis, or pregnancy disease, can ordinarily be eliminated from further consideration unless losses have also occurred among pregnant ewes.

So-called feedlot hyperglycemia, or "overeating disease," also occurs in all classes of sheep, but lambs are especially susceptible. As sudden death characterizes this disease, it should not be confused with ketosis. Also, the urine is free from ketone bodies and sometimes contains a large amount of sugar.

The autopsy findings are also helpful in diagnosing ketosis in a flock of breeding ewes. As in the cow, a positive test for ketone bodies in urine of a pregnant ewe should not be regarded as without some significance even tho definite symptoms are not detectable. The syndrome may be in the very early stage.

Treatment

In a discussion of the physiologic basis of therapy for ketosis in the ruminant, Sampson and Boley[107] say:

> It was recognized early in the study of ketosis in ruminants that all forms of treatment were ineffective for the advanced stage of pregnancy disease in sheep. The results of dextrose therapy, however, were sufficiently encouraging to warrant further trials with this agent. These trials have clearly demonstrated that a liberal administration of dextrose or similar carbohydrate is often highly effective for ketosis in pregnant ewes provided (1) the treatment is begun during the early stage of the disease, and (2) oliguria, anuria and other complications have not developed.

Poor results with carbohydrate therapy, which seems to be as specific for ketosis in the ewe as in the cow, can usually be explained on the basis that treatment was either *started too late* or that *it was not continued long enough.* Flock owners often fail to call a veterinarian to make a diagnosis until several ewes have died and others are in the advanced stage of the disease. *It cannot be emphasized too strongly that early diagnosis and prompt treatment are imperative for favorable*

results with any form of therapy in ketosis of pregnant ewes. The cost of treatment may become prohibitive if daily injections of dextrose are administered by a veterinarian, but such a procedure is neither necessary nor desirable. After one injection perhaps, subsequent treatment can be carried out by careful drenching. For this purpose several ounces of either molasses, sorghum, corn sugar, or other concentrated carbohydrate can be diluted with a pint of water and given by the owner with an ordinary 2-ounce syringe. Two or more treatments daily are recommended until the appetite is restored. If the attack is not too severe and if it develops a short time before parturition, recovery with or without treatment often occurs after the lambs are born.

Groenewald *et al.*[45] also recommend the use of carbohydrate therapy in ketosis of the ewe, but caution that this may not be entirely effective. These investigators state: "It can be understood, therefore, that the administration of glucose alone will not be expected to cure all the symptoms of domsiekte, but its use is rational and strongly indicated."

Clark, Groenewald and Malan,[21] in a report published in 1943, call attention to the need for increasing peristalsis as well as to the need for sugar. They state:

> It is considered that the main object to be attained in any treatment is to get purgation. It has been noted that ruminal atony and constipation of the large intestine is an almost constant finding in cases of domsiekte and no permanent improvement can be expected till this is relieved. Lentin acts well but 120 cc. of raw linseed oil has also been found effective. Rapidly absorbable carbohydrate such as glucose or sugar is . . . indicated.

At the present time if treatment is attempted, the administration of glucose or similar carbohydrate has largely replaced other forms of therapy. Groenewald *et al.*[45] mention insulin, calcium carbonate, calcium gluconate, formaldehyde, adrenalin, sodium bicarbonate, and bone meal as other agents besides glucose which have been employed by various investigators in treating ketosis of sheep. Roderick and Harshfield,[99] in addition to some of the substances mentioned, administered solutions containing either calcium chloride or magnesium sulfate without any apparent benefit.

Recently it has been suggested that vitamin A therapy may be indicated for ketosis in ewes.[39] On the basis of the negative results obtained by Shaw *et al.*,[121] Hayden *et al.*,[48] and Hendershot[50] with vitamin A therapy in ketosis of the bovine, it does not seem likely that it will prove any more effective for ketosis in sheep. Furthermore, Barron[5] and Underwood, Curnow, and Shier[138] have shown that the vitamin A content of livers of ewes affected with pregnancy disease is about the same as that in livers of healthy ewes. Underwood and his

associates conclude that it appears "extremely unlikely that vitamin A deficiency can have anything to do with the incidence of pregnancy toxemia."

Prevention

For many years after pregnancy disease was first recognized, lack of agreement continued as to the measures that might be taken to prevent the disease;[45] but now that the etiology is established beyond reasonable doubt, the problem has become fairly simple.

The lack of agreement on prevention is explained by the fact that even tho pregnancy disease was found not to be caused by infection and was believed to be the result of improper feeding, knowledge of its occurrence in both adequately and inadequately fed ewes resulted in a confusion of ideas concerning methods of feeding to prevent it. For example, flock owners were often advised to reduce the ration in advanced pregnancy, a practice which we now know is usually contraindicated because, as mentioned on page 441, the sudden decrease in feed consumed, irrespective of cause, leads to an attack of ketosis and symptoms of pregnancy disease in well-nourished ewes. If pregnancy disease develops in a flock that is fed a liberal ration, it is frequently advantageous to feed a small amount of molasses (see page 426). Hull[54] recommends that under such circumstances a ration of yellow corn and alfalfa hay "may be supplemented by three quarts of molasses per hundred ewes per day for three or four days." Some flock owners feed a small amount of molasses thruout the greater part of pregnancy.

In general, pregnancy disease rarely becomes a problem in flocks that are well fed, especially if ewes are fed liberally during the last third of pregnancy. The experience of many farmers who have kept a breeding flock of sheep for a number of years clearly demonstrates that if each ewe is fed a daily ration of about 1 to 1½ pounds of concentrates, such as equal parts by weight of shelled corn and whole oats, and at least an equal amount of good-quality legume hay during the last 6 to 8 weeks before lambing, the incidence of ketosis may be expected to be very low.

As mentioned on page 441, most cases of pregnancy disease in sheep occur in flocks that are underfed. In most outbreaks of the disease it is found that the breeding flock is in poor condition and losing weight despite a sincere belief on the part of many owners that the ewes are in good flesh. Increasing the ration usually is all that is needed to stop further losses from ketosis in these flocks.

Attention has been called (page 438) to the observation that clinical ketosis is not diagnosed as often in cows that have access to *good*

pasture as in stabled animals. This observation also applies to sheep because pregnancy disease is not a problem in ewes that lamb during the months when the flock has access to an abundance of succulent grass or legume pasture.[a]

All pregnant animals should have a moderate amount of exercise thruout pregnancy. Ewes are no exception.

KETOSIS IN GOATS

Forbes[38] has reported some interesting results on experimental ketosis in goats. (Lukens[70] has shown that pancreatectomy causes a mild diabetes in this species.) Forbes investigated the effects of inadequate caloric intake on blood sugar and blood ketones in two goats during pregnancy and lactation. Forbes found that:

> The blood sugar values under the low-calory treatment reached minimum figures of 28 mg. per 100 cc. during late pregnancy, 32 mg. during early lactation, 46 mg. after 11 weeks lactation, and 24 mg. during early pregnancy. These figures may be contrasted with the normal values of 45-60 mg. . . . The ketone levels for the blood of the goats under the low-calory treatment reached maximum values of 25 mg. per 100 cc. during late pregnancy, 18 mg. during early lactation, 4.0 mg. after 11 weeks lactation, and 3.7 mg. during early pregnancy. These figures may be contrasted with normal values of 2-4 mg.

Forbes' results with pregnant goats are somewhat comparable to the results obtained by Fraser *et al.*[40] with pregnant ewes (see page 421).

Gilyard and Gilyard[43] have described typical clinical ketosis in the goat. Their report refers to observations made in a herd of goats, in which twelve fatal cases occurred among pregnant does. The herd had been fed mixed hay but no grain. Paresis and coma, with normal body temperature, were characteristic symptoms. The urine of one sick doe was found to contain 450 mg. of ketones per 100 ml. Treatment with 10-percent glucose, 1 liter given subcutaneously and 300 ml. given intraperitoneally, lowered the ketonuria but was not effective in saving the doe. No more cases developed after the tenth day following the addition of grain and molasses to the ration. The data would have been more complete had analyses been made for blood sugar and blood ketones; yet the symptoms, severe ketonuria, and the apparent beneficial effect of adding grain and molasses to the ration are almost certain proof that these goats were affected with spontaneous ketosis and hypoglycemia.

[a] Rations for pregnant ewes are given in Illinois Circular 532, "The Sheep Enterprise."

II. KETOSIS IN OTHER DOMESTIC ANIMALS

KETOSIS IN THE SOW

Our knowledge of ketosis in swine is limited because it has been known for only a relatively short time that spontaneous ketonemia occurs in this species. Credit for this important observation belongs to Hull and Nolan[55] who, in 1940, described three cases which had been diagnosed in the Department of Animal Pathology at the Kentucky Agricultural Experiment Station.

In 1943 Sampson and Hanawalt[111] published data which apparently confirmed the earlier findings of Hull and Nolan. The data of Sampson and Hanawalt were obtained in the course of observations of a peculiar disorder in a sow which had been correctly diagnosed by a practicing veterinarian as uncomplicated ketosis, or acetonemia. So far as is known, this was the first report of ketosis in swine to be made from Illinois. Furthermore, so far as the author is aware, spontaneous ketosis in swine has been reported from only one other state (New York)[22] besides Kentucky and Illinois.

Biester,[8] of Iowa, in 1925 described a condition in a pig weighing approximately 25 pounds which he believed to be diabetes mellitus, The diagnosis was based on evidence of severe glycosuria, 6.6 percent, and a marked lowering of the pig's tolerance for sugar. On autopsy of the pig, histopathologic examination of the tissues revealed that the cells of the islands of Langerhans in the pancreas were atrophic and degenerated. The report fails to mention whether tests were made for evidence of ketosis.

Only limited study has been made of experimental ketosis in swine. There are probably a number of reasons for this, but the belief expressed by Woods[142] that the pig "has a low liability to ketosis" is possibly the most important one. Woods so concluded when he failed to find evidence of ketosis in a 20-pound pig at the end of a fast of 11 days. That young pigs have indeed a low liability to ketosis apparently has been confirmed by Hanawalt and Sampson,[46b] who found that no significant ketonemia or ketonuria developed in pigs weighing approximately 30 pounds even after they were deprived of all food (but not water) for as long as 28 days. Nevertheless, since it has been found that spontaneous ketosis occurs in the porcine species, further study of the effect of fasting and of certain other influences on the concentration of ketone bodies and of certain other constituents in

blood of swine of different ages and under various experimental conditions is highly desirable.

Evidence so far available seems to indicate that spontaneous, or natural, ketosis in swine is not often associated with diabetes mellitus and it is significant, perhaps, that experimental pancreatectomy apparently causes only a mild form of diabetes in this species.[69]

Reference to the report by Hull and Nolan[55] of clinical ketosis in swine will be restricted to their observations on two cases inasmuch as the values for blood and urine ketone bodies in Case 3 seem hardly large enough to warrant a diagnosis of either ketonemia or ketonuria. In Case 1 symptoms of ketosis developed in a Poland China sow, weighing about 160 pounds, at approximately the seventh week after farrowing. The ration fed before farrowing was composed of corn and tankage, while after farrowing the sow received about ½ pint of tankage and 3 to 6 ears of yellow corn each day. The amounts of tankage and corn fed before farrowing are not given. The sow had had access to "scant pasturage." An extraordinarily rapid loss of body weight and lameness were prominent symptoms, according to the owner, within three weeks after farrowing. Hull and Nolan state that the history and symptoms were suggestive of posterior paralysis. They mention also that a post-mortem examination of the sow revealed pathologic changes in the liver and kidneys, presumably of the nature of fat phanerosis.

In Case 2 ketosis was demonstrated in a three-year-old sow at approximately one month post-partum. A decrease in body weight from 400 pounds to 275 pounds had occurred in this period. The ration fed during pregnancy is not mentioned, but after farrowing the sow was given 3 to 4 ears of corn and some tankage each day. This sow also had had access to "scant pasturage." The sow was not far from death when submitted for diagnosis and was therefore killed. At autopsy, changes in the liver and kidneys were found similar to those observed in Case 1.

Hull and Nolan do not include data on the concentration of the ketone compounds in the blood and urine of normal swine, but Hanawalt and Sampson (*unpublished data*) have found that blood and urine of healthy pregnant and lactating sows contain only traces of ketone bodies.

The description of the symptoms and results of chemical determinations on blood and urine given in the report by Sampson and Hanawalt of ketosis in the sow are quite similar to those already known to characterize uncomplicated ketosis in the cow and ewe. Hypoglycemia does not seem to be as severe in the sow as in the cow

and ewe, but further study is needed before a definite statement can be made with respect to this point.

Observations on ketosis of swine at the Illinois Agricultural Experiment Station have thus far been limited to four cases diagnosed in sows during the early part of lactation. This group of four animals includes the sow referred to in the report by Sampson and Hanawalt. Two of the sows were from the same farm in Illinois, while another, found to be affected with what appeared to be uncomplicated ketosis, originated in a herd of swine in a neighboring state. One veterinarian reported that several sows had died before he submitted a typically affected animal to the laboratory for diagnosis.

Several or all of the following symptoms were observed in the four sows: lack of appetite, rapid loss of body weight, wobbly gait, and varying degrees of somnolence. In uncomplicated ketosis the body temperature was normal. Respiration did not seem to be noticeably affected. Sows that developed ketosis seemed to be "good milkers" (Fig. 7), but no critical evidence was obtained to verify this observation.

With reference to the cause of ketosis in swine, Sampson and Hanawalt[111] made the following statements:

It seems probable that the fundamental cause is the same whether ketosis occurs in cows, ewes, or sows; namely, an insufficient intake of readily available carbohydrate or potential carbohydrate material. Under certain circumstances, such as late pregnancy and the early stage of lactation, an inadequate intake of concentrated carbohydrate in the form of starches and sugars might be due to various causes. For example, either inappetence (associated with constipation or a digestive disturbance of any form), or a marked decrease in the daily feed allowance would reduce the carbohydrate intake. Any appreciable decrease in daily feed consumption would

Ketosis (acetonemia) in a sow several days after farrowing. (a) During the attack; (b) six weeks later, when the sow had recovered and was still nursing a litter of ten pigs. (Fig. 7)

TABLE 4. — TOTAL KETONE BODIES AND SUGAR IN BLOOD OF HEALTHY SOWS AND SOWS AFFECTED WITH CLINICAL KETOSIS

(Ketone bodies expressed as acetone)

Healthy sows[a]			Sows affected with ketosis[b]		
Sow	Ketone bodies	Sugar	Sow	Ketone bodies	Sugar
	mg/100 ml	mg/100 ml		mg/100 ml	mg/100 ml
1	Trace	56.50	5	68.20	61.02[c]
2	Trace	40.68	6	36.08	58.76
3	Trace	80.23	7	95.23	79.10
4	Trace	71.19	8	41.17	54.24

[a] Sows 1 and 2 were in late pregnancy, and Sows 3 and 4 in early lactation.
[b] Sows 5, 6, 7, and 8 were in early lactation.
[c] This value was obtained in analysis of blood collected 24 hours after subcutaneous injection of 125 grams of dextrose.

soon be reflected in a decreased glycogen supply stored in the liver. Such a condition, as Mirsky[82] points out, could result in an increase in the oxidation of fatty acids in the liver and excess production of ketone bodies.

The etiology of ketosis in swine is a challenging problem for further research.

Illinois data on the concentrations of ketone bodies and sugar in blood of healthy sows and sows affected with ketosis are shown in Table 4. The data reveal that values for blood ketone bodies in spontaneous ketosis of the sow may be as high as or higher than values often obtained in determinations for ketone bodies in blood of cows and ewes affected with severe ketonemia.

On the basis of the data given in Table 4 for blood sugar, it might be inferred that hypoglycemia is not associated with ketosis in swine. That such an inference probably is not correct is indicated by the observations of Hull and Nolan, who found that hypoglycemia (20 mg. percent) is sometimes as severe in ketosis of the sow as it is in some cases of ketosis in the cow and ewe. Further study of spontaneous ketosis in sows is needed, however, to determine the frequency and the intensity of hypoglycemia in this species. Apparently normal concentrations are found for calcium, magnesium, inorganic phosphorus, hemoglobin, nonprotein nitrogen, and chlorides of the blood of sows affected with ketosis, but more observations are needed before a definite statement can be made.[111]

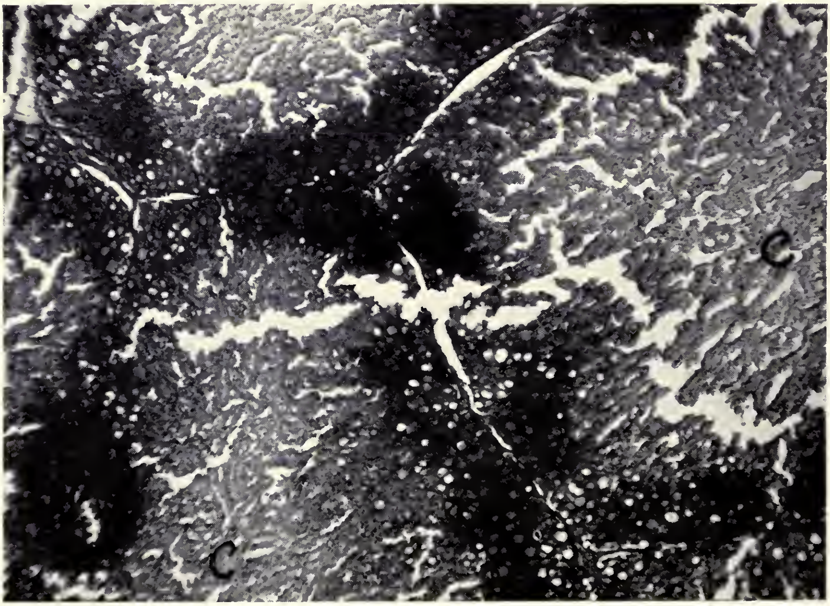
Knowledge of the histopathology of ketosis in swine is also limited. Reference has been made to the observations reported by Hull and Nolan. Morrill has made a careful study of gross and microscopic changes in tissues of several sows affected with ketosis and has summarized his findings (*unpublished*) as follows:

The pathological changes found in the livers and kidneys of the few cases of porcine ketosis coming to autopsy at the Illinois Station have resembled rather closely those described for sheep and cattle.

The liver in general is not visibly enlarged, but is pale yellow to ochre in color and friable, and the cut surface imparts a greasy film to the knife. The discoloration may be completely diffuse or may vary within the lobule, the periphery being yellow and the central portion reddish brown. Microscopic examination of sections of livers in which lipoidal substances have been retained and stained with a fat-soluble dye reveal the presence of fatty changes, either diffuse or more marked near the periphery of the lobules [Fig. 8].

The kidneys also show diffuse yellowish discoloration of variable degree. Application of histological procedures to demonstrate the presence of lipoidal material reveals widespread fatty changes in the epithelium, particularly in convoluted tubules and to a considerable extent in collecting tubules.

Treatment and prevention. There is some evidence that therapeutic and prophylactic measures recommended for ketosis of the cow and ewe are just as applicable for ketosis of the sow, but more information is needed.[111]



Section from liver of sow with ketosis. Greater concentration of fat occurred in peripheral parts of the lobules. C = central vein. Sudan IV-hematoxylin. × 40. (Fig. 8)

KETOSIS IN RABBIT, CHICKEN, AND DUCK

Only limited information is available on the susceptibility of other domestic animals to spontaneous and experimental ketosis, particularly ketosis caused by fasting or by inadequate consumption of antiketogenic food. Hunger causes ketonuria in the rabbit,[17] and Sampson and Dukes (*unpublished data*) found that fasting may produce an appreciable ketonemia in well-nourished hens. Similarly, Mirsky, Nelson, Grayman, and Korenberg[83] found that fasting causes a rapid accumulation of ketone bodies (up to as much as 45 mg. percent) in the blood of normal ducks.

On the other hand, whereas pancreatectomy produces typical diabetes accompanied by ketosis in the rabbit,[135] this operation produces at most only a mild form of diabetes in the chicken[64] and duck.[131, 83] (Batt, cited by Dukes,[28] found that the fasting chicken has an average blood sugar concentration of approximately 185 mg. percent and confirmed the observations of others that pancreatectomy does not cause severe diabetes in this species.)

KETOSIS IN DOG AND CAT

The adult dog has been found to be comparatively resistant to the development of ketosis during fasting.[1, 25] It is not clear from the literature, however, to what extent the pregnant bitch has been used in studies of the relation of fasting to ketosis in dogs. Apparently fasting may cause hypoglycemia in the well-nourished lactating bitch.[77] Puppies, in contrast to older dogs, develop a marked ketosis with fasting.[1]

Phlorhizin administration and pancreatectomy have been the two common procedures employed in producing experimental diabetes mellitus in the dog.[1] The administration of anterior pituitary extract[34, 143] and alloxan[30] are newer technics of producing experimental diabetes and its attendant symptoms.

On the basis of evidence now available it would appear that spontaneous or clinical ketosis is of rare occurrence in dogs.[57] Furthermore, when it is observed it is apparently associated with diabetes mellitus. The literature contains a number of references to diabetes mellitus in dogs, but evidence on which the diagnosis of the disease was made is often lacking. Milks and Stephenson[80] published a report on several cases of diabetes in dogs and included in their description of each case results of chemical determinations on blood and urine and observations made at autopsy of affected animals.

The data of Milks and Stephenson revealed that hyperglycemia, ketonemia, ketonuria, and glycosuria characterized these cases. An apparent complete lack of pancreatic tissue in three of the dogs provided additional evidence in support of the diagnoses. A summary of the data reported by Milks and Stephenson is given in Table 5.

TABLE 5. — TOTAL KETONE BODIES AND SUGAR OF BLOOD AND URINE IN DIABETES MELLITUS OF DOGS[a]

(Ketone bodies expressed as acetone)

Dog	Blood		Urine		Comment on condition of pancreas at autopsy
	Ketone bodies	Sugar	Ketone bodies	Sugar	
	mg/100 ml	mg/100 ml	gm/100 ml	gm/100 ml	
1..........	22.63	435	.29	6.11	No pancreas could be found.
2..........	.....	513	...	High	Pancreatic tissue less than 1 cm. in diameter.
3..........	.....	...	...	4.00	Pancreas largely replaced by scar tissue and fat.
4..........	.....	328	...	1.37	No pancreatic tissue could be found.
5..........	.....	...	...	40.00	(Pancreas not mentioned.)
6..........	.....	400	...	....	Pancreas has practically disappeared.
7..........	4.09	...	.32	1.36	Pancreas appeared normal.
8..........	.....	...	...	6.25	Pancreas replaced by connective tissue.
9..........	26.32	260	...	3.33	No pancreatic tissue could be found.

[a] From data of Milks and Stephenson. Cornell Veterinarian **27**, 169-177 (1937).

Pancreatectomy causes severe diabetes in the cat,[68] but presumably little is known concerning the incidence of spontaneous ketosis in this species.

KETOSIS IN THE HORSE

So little information is available on ketosis in the horse that further reference to the condition in this species is hardly justified. The concentration of ketone bodies in the blood of normal horses is presumably the same as for other domestic animals.

Illinois studies showed only a trace of ketone bodies in the blood of nine healthy draft horses. These horses consisted of 2 mares not pregnant, a mare to foal in 10 days, one foaled 10 days before, one bred two weeks before, a filly not pregnant, and 3 geldings. Another mare, not pregnant, showed 5.08 milligrams of ketone bodies per 100 milliliters (expressed as acetone).

Future studies may reveal that pregnant and lactating mares are as susceptible to ketosis as the cow, the ewe, and the sow.

SUMMARY

The foregoing discussion reviews and appraises the rapidly growing knowledge on clinical (spontaneous) and experimental ketosis in domestic animals, with special emphasis on ketosis of the cow, the ewe, and the sow. Evidence so far accumulated seems to indicate that the theory of "antiketogenesis" is as applicable to domestic animals as it is to humans.

The economic importance of clinical ketosis in cattle and sheep is now recognized in most, if not all, parts of the world. Cows affected with severe ketosis (acetonemia) often show a 50-percent or greater reduction in milk production. Furthermore, if proper treatment is not given, they may become worthless or die. Death losses from clinical ketosis (pregnancy disease) in sheep are high, since 90 percent of affected ewes ordinarily succumb unless treatment is begun during the early stage. Lambs, if born, are usually unthrifty and often do not survive.

Experimental ketosis, apparently indistinguishable from clinical ketosis, may be induced in cows and ewes by subjecting the animals to partial or complete inanition. Animals that are (**1**) fat, (**2**) nearing parturition, or (**3**) in early lactation are most susceptible.

The chief pathological changes in tissues and organs of cows and ewes succumbing to ketosis are usually limited to the liver and kidneys. The liver has a yellow color and contains an enormous amount of fat; while the kidneys, besides having a high fat content, often show degenerative changes.

The cause of death of cows and ewes that die of what is believed to be uncomplicated ketosis has not been determined, but disturbed carbohydrate-fat metabolism in the liver, functional damage to the central nervous system, and impaired kidney function may be important contributing influences.

Many products have been used in treating ketosis of the cow and ewe. The most effective seems to be some form of concentrated carbohydrate such as glucose.

Evidence now available seems to indicate that two conditions are essential in preventing clinical ketosis in the pregnant or lactating cow and ewe (and in all probability in the goat and sow as well): (1) an adequate daily ration of nutritious feeds and (2) a good appetite on the part of the animal.

Clinical and experimental ketosis in the goat and sow presumably are fundamentally similar to clinical and experimental ketosis in the

cow and ewe, but further study is needed before definite conclusions are warranted. The extent of spontaneous ketosis, if it occurs, in other domestic animals, specifically in the pregnant or lactating female, such as the mare and bitch, has not been established.

Information of great value has resulted from clinical and experimental observations made during recent years, but additional study is necessary for a clarification and more complete understanding of many aspects of ketosis in animals.

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